FIFRA SCIENTIFIC ADVISORY PANEL (SAP)

OPEN MEETING

SCIENTIFIC ISSUES ASSOCIATED WITH THE

AGENCY'S PROPOSED ACTION UNDER FIFRA 6(b)

NOTICE OF INTENT TO CANCEL CARBOFURAN

U.S. ENVIRONMENTAL PROTECTION AGENCY

CONFERENCE CENTER- LOBBY LEVEL

ONE POTOMAC YARD (SOUTH BUILDING)

2777 SOUTH CRYSTAL DRIVE

ARLINGTON, VIRGINIA 22202

FEBRUARY 6, 2008

8:32 A.M.

U.S. ENVIRONMENTAL PROTECTION AGENCY

FIFRA SCIENTIFIC ADVISORY PANEL (SAP)

OPEN MEETING

February 6, 2008

DR. MATTEN: Good morning. We're going to start the second day or our meeting on carbofuran issues. My name is Sharlene Matten. I work in the office of Science Coordination and Policy. I'm the designated federal official for this meeting. We're going to continue our discussions that follow Dr. Reaves' presentation yesterday. And I'm going to turn the floor over to Dr. Heeringa, who will then continue leading the panel through the various discussions. Thank you.

DR. HEERINGA: Good morning, everyone, and welcome back to the second day of our multi-day session of the FIFRA Science Advisory Panel; addressing the topic of scientific issues associated with the Agency's proposed action under FIFRA 6 (b) -- Notice of Intent to Cancel Carbofuran.

I am Steve Heeringa of the University of Michigan. I am the President Chair of the FIFRA Science Advisory Panel. Today, we're joined, as yesterday, by an expert panel, to address the specific charge questions and scientific issues associated with

this meeting topic.

I'd like to have them introduce themselves again this morning, beginning with Dr. Chambers.

DR. CHAMBERS: I'm Jan Chambers with the College of Veterinary Medicine at Mississippi State University. And I'm a member of the permanent panel. My area of expertise is pesticide toxicology.

DR. HANDWERGER: I'm Stuart Handwerger. I'm Professor of Pediatrics and Cell and Cancer Biology at the University of Cincinnati College for Medicine. I'm and endocrinologist whose primary research is in molecular and developmental biology.

DR. PORTIER: Good morning. I'm Ken Portier, Director of Statistics, the American Cancer Society National Home Office in Atlanta. And I'm a member of the permanent panel.

DR. SCHLENK: My name is Dan Schlenk. I'm a professor in the Department of Environmental Sciences at the University of California, Riverside. My area of expertise is aquatic toxicology and I'm a member of the permanent panel.

DR. CLARK: My name is Larry Clark. I'm the Assistant Director of the USDA's National Wildlife Research Center. And my areas of expertise are wildlife oncology, sensory biology and wildlife

diseases.

DR. DELORME: Good morning. My name is Peter Delorme. I'm currently Acting Director of the Environmental Assessment Director of the Pest Management Regulatory Agency at Health Canada.

DR. GRUE: Good morning. My name is Chris Grue. I'm leader of the Washington Cooperative Fish and Wildlife Research Unit, University of Washington. My area of expertise is fish and wildlife toxicology.

DR. HILL: I'm Elwood Hill. I am a wildlife toxicologist. My area is primarily organic phosphorus, carbamate and mercury toxicology.

DR. MCCARTY: My name is John McCarty. I'm a Professor of Biology at University of Nebraska at Omaha. I'm an ecologist, and specialize in the ecology of birds.

DR. MONTGOMERY: I'm Cheryl Montgomery. I'm a consultant with Montgomery and Associates. I am a chemist, and I practice risk assessment.

DR. SAMPLE: I'm Brad Sample -- CMSM HILL, ecological risk assessor.

DR. SPARLING: Don Sparling with Cooperative Wildlife Lab in Department of Zoology at the Southern Illinois University. My area of expertise

is wildlife toxicology.

DR. STINCHCOMB: Audra Stinchcomb, University of Kentucky, College of Pharmacy. I'm an associate professor there. And my area of expertise is dermal absorption.

DR. REED: Nu-may Ruby Reed. I'm with the California Environmental Protection Agency. I do pesticide health risk assessment.

DR. MACDONALD: Peter Macdonald, Professor of Mathematics and Statistics at McMaster University in Canada. I have general expertise in applied statistics.

DR. LU: Alex Lu from Rollins School of Public Health at Emory University. I do human exposure to pesticides and the hazard factor and biomarkers.

DR. KEHRER: Jim Kehrer, Dean of the College of Pharmacy at Washington State University. I'm in molecular toxicology.

DR. HATTIS: Dale Hattis, Clark University. I specialize in issues of uncertainty and variability in mechanistic modeling.

DR. EDLER: Lutz Edler, German Cancer Research Center -- head of the Bio-statistics Department there, and responsible for experimental and clinical studies, and also interested in risk

assessment.

DR. BUNGE: Annette Bunge. I'm a Professor at Chemical Engineering at the Colorado School of Mines, and I specialize in dermal absorption issues and risk assessment.

DR. BAILEY: Ted Bailey, Department of Statistics at Iowa State University.

DR. HEERINGA: Thank you very much, again, members of the panel. Before we begin, just a little synopsis of where we are in the agenda. If you're joining us for the first time today. We do have a floating agenda that is currently scheduled over four days -- or three-and-a-half days. We are about two or three hours behind the posted times on the agenda. I guess I anticipated that. We are in the process of hearing and asking questions of clarification of the EPA scientific staff of their presentations. After that, we'll turn to the period of public comment, and it will be an extensive period of public comment today.

Throughout this process, it's my intent that we fully develop each of these issue and have appropriate time to ask these questions of clarification. So, I would anticipate us to sort of remain behind the agenda schedule today; probably about the same lag that we experienced yesterday.

It's also my current thinking in terms of planning for the week that I anticipate that we will, in fact, return Friday morning for a continuation and a wrap-up of this session on Friday -- just based on my experience with these and the fact that I don't intend to have us rush through things. This is a very serious matter here. We want to make sure we have full development and exploration.

So, with that, this morning, I'd like to turn to Dr. Debbie Edwards or to Steve Bradbury possibly for some opening comments.

DR. BRADBURY: Thank you, Dr. Heeringa. Again, welcome to the panel and I'm looking forward to the second day of discussions. I know there's a couple of follow -up -- at least one set of follow-up questions that we want to handle shortly with regard to drinking water half-life question and we'll cover that. And then, I believe we'll continue with clarifying questions.

There's one topic that came up yesterday a couple of times, and if I could just touch on that very briefly. It has to do with the conditional label changes that the registrant has submitted. And I know a couple of times there were panel members that had some questions about that.

The proposed label changes that were submitted to the Agency in mid-December include continuing, I believe, four uses, but also, adding a new use for their further use of the product on cotton. And that requires -- that would be a new use, a new registration, and would require both an ecological and dietary risk assessment. And that goes through a process. It typically takes for a new use about twelve to fifteen months to go through the process of that evaluation.

So, it's important to realize that some of these changes on the current label are contingent upon the addition of a new use. So it isn't a use by use proposal that was submitted to the Agency. It's sort of package deal. It includes adding further use on cotton in addition to reducing a number of uses that are currently on the label.

Now, having said that, I believe the charge questions or the issues that the Agency's focusing on in terms of ecological risk and human health risk, and the feedback we'll get from the panel will be helpful regardless of whatever you chair -- use patterns -- may or may not occur for carbofuran.

On the context of human health risk assessments, as we were starting to discuss yesterday,

the Agency's primary interest in getting feedback from the panel concerns aspects of the cholinesterase. How to take a look at red blood cells versus brain. How to be taking a look at the dose response curves for those response. How to think about oral route to dermal route extrapolation -- those kinds of issues, which will be important regardless of what food-use pattern may exist or not exist for carbofuran in the future. Certainly the overall dietary exposure that could exist with a different pattern of uses will change, but the underlying interpretation of the cholinesterase inhibition and -- and the various extrapolation issues are sort of even dependant of what the uses would be at the end of the day. So we don't think that has a major impact in the deliberations we'll be having in the next few days.

In terms of the ecological risk assessment, as we discussed yesterday, the risk assessment is focused at a spacial scale of the field. And, so, you're looking at the scenarios that have been done thus far for the ecological risk assessment while there's alfalfa and corn being used as a surrogate, the idea is -- or the issue is that those are spanning a range of use patterns that transcend the use patterns that are on the label in terms of application rates,

and kinds of application methodologies, and the alfalfa analysis, for example, isn't a water fowl risk assessment, it's a risk assessment on passing birds in row crops.

So alfalfa and corn are being used as surrogates for row crops across a span of application rates, application methods, and trying to get handle on how to estimate risk on a field where carbofuran or foliar carbofuran has been applied.

So, again, from the Agency's perspective understanding how to interpret studies to try to get at matrix effects on carbofuran potency. Trying to understand how to take into account recovery of cholinesterase in brain tissue of birds in terms of the probabilistic risk assessment -- how to interpret incidents data or field studies with foliar carbofuran -- how to interpret the risk quotient methodology in assessing the potency of carbofuran to birds in many ways transcends what use patterns may exist in the future.

So all the use patterns may change. The underlying fundamental scientific issues in assessing the risk transcend the use patterns to -- in the Agency's opinion. And so we think that as we move forward in the charge questions we'll get useful

information, regardless of what the use patterns may or may not be in the future.

If there are any follow-up questions, I'll be happy to handle that. But then maybe we could move into the clarifying questions from the Human Health Topic.

DR. HEERINGA: Thank you very much, Dr. Bradbury.

Dr. Brimijoin?

DR. BRIMIJOIN: Could I ask a follow-up question? Supposing that the Notice of Intent to Cancel is, in fact, carried through to cancellation, and yet the company has a new-use application pending -- I mean, is there -- what would -- is there an open procedure for them to go forward with the request for a new registration, let's say for cotton -- providing, of course, new data to convince EPA then, in fact, the product is safe?

DR. BRADBURY: Yeah, there is a -- there is a process to do that. When -- and Debbie you could help me, or GC could help me, but I believe if we go through a process then it's cancelled there is a process whereby a cancelled pesticide can have a use come forward, but there's a process that you have to go through to do that.

MR. HEERINGA: Okay, let's return then to the presentations yesterday afternoon from Jack Housenger and Anna Lowit and Elissa Reaves on the human health risks. And I know that there have -- certainly are some residual questions from this afternoon and some new questions that may have occurred to people as they thought more about this last evening.

Dr. Bunge, you had a question before we -- are we ready to go?

DR. LOWIT: We had a couple follow-ups from yesterday.

DR. HEERINGA: Okay. Well, let's

DR. LOWIT: Do you want us to start with those?

DR. HEERINGA: -- do those to start with, please.

DR. LOWIT: And, I believe David Jones also had a follow-up from yesterday on the --

DR. HEERINGA: Please, go ahead then.

DR. LOWIT: I'll start and then Dick can go, and then return it back to the panel.

(WHEREUPON, conversations took place off the record.)

DR. LOWIT: There was a question from a Dr. Hattis conceptually around biological time -- the differences between rats and humans. And as we stated

previously as part of review of the review board, you won't hear us talking about the carbofuran human study, however, there are three human studies for carbamates that did go through the review of the HSRB and were okayed for use in the risk assessment. And they do provide some context for that question. And I've got some tables in front of me with the parallel rat data. So just in sort of basics of those studies they're each ascending -- ascending acute single doses with the number of subjects ranging from somewhere in the order of twenty to thirty or fifty.

They each have pretty good time course ranging from a few minutes after post-dose up to the following day. Clinical signs, as we said yesterday, it's very difficult to match clinical signs with cholinesterase inhibition. In some ways that's a very chemical specific situation. You can have some carbamates where you get signs of very low levels of inhibition and others where you see clinical signs they don't sort of kick in, for a lack of better term, until much greater inhibition.

But the question from Dr. Hattis was around the half-life in a relationship between the humans and the rats. So you see the last two levels here in this slide that Dr. Reaves put together (Indicating.), the

half-life for each of those is roughly about two hours with decent confidence limits of a little bit less -- about an hour -- somewhere in the order of three to four hours. And with regard to the rat for those three compounds, just as point of comparison, in the adult rat, I didn't have at my fingertips quickly this first thing this morning, the RBC numbers, but brain and RBC are usually not that different.

For aldicarb in the adult rat, the recovery half-life is an hour-and-a half. For methomyl, it's between three-quarters of an hour and an hour depending on the study. For oxamyl it's approximately an hour. For both methomyl and oxamyl, they tend to have -- both of those compounds have very strong data bases, and the confidence limits on the rat numbers are very tight -- arranging from about half-an-hour to one-and-a quarter-hours for both.

For aldicarb, the confidence limits on the half-life range from about an hour to about two hours. So, still pretty tight. So, regarding -- at least in adults, I would say that the rats and the humans are pretty comparable of about two hours.

For the pups, for methomyl and oxamyl in rats, for methomyl, the half-life in a PND 11 brain is about -- roughly half-an-hour -- point four hours, so

about half-an-hour. I don't have the confidence limits. And oxamyl, the half-life is about an hour-and-a half. But if we look across the carbamates, and this is a table right out of the accumulative -- it's more like other situations that -- keep in mind it's a dose dependent situation. So, it ranges in the table. The low being methomyl about point four hours, the high being fermintinite of about nine hours. So what we call sulpha-carbofuran is somewhere in between those.

I think I had --

MR. HATTIS: So why? Carbofuran is a little unusual in having an appreciatively different half-life for the pups versus the adults?

DR. REAVES: I wouldn't say it's appreciable. I'm not sure if we have enough data to really set a trend. But what we do know from the pups is that the range across the class is much greater than what's seen in the adults. The range in the pups across the class, we got -- I've got data for five chemicals, carbaryl, carbofuran, fermintinite, methomyl and oxamyl. The shortest being methomyl of point four, the longest being fermintinite of nine, carbofuran is in the middle there (Indicating).

DR. HATTIS: So, there is a tendency for the pups to be longer half-lives -- shorter -- lessor

inhibition rates then the adults in the examples we have in front of you.

DR. REAVES: Yes, yes, with caveat that there's a dose dependance to it.

DR. HATTIS: Yes.

DR. REAVES: And we would have to go back to see

DR. HATTIS: Yes.

DR. REAVES: inhibition

DR. HATTIS: Right.

DR. REAVES: -- was in the studies to make sure you're comparing apples and apples.

MR. HATTIS: Right.

DR. REAVES: I think we had one more slide. Just of point of transparency, I'd shown a plot yesterday out of the 2005 --

(WHEREUPON, conversations were held off the record.)

DR. LOWIT: I had shown a plot yesterday out of the 2005 preliminary accumulative assessment for the carbamates. Making two points -- one of them was a derivation of the original five factor for the 2006 risk assessment, the other one where I was trying to make the point that aldicarb and carbofuran really aren't that different of potency. Just for point of transparency so the panel has a more recent

information, we pulled these plots -- this plot and the next one (Indicating.), excuse me, out of the 2007 revised assessment, which includes updated data for most compound including carbofuran. So there are two of them. The first one is for RBC -- go back -- you can see the blue dots where the aldicarb and carbofuran were essentially the same; so they are similar in potency when you compare apples and apples with regard to the brain. You can see carbofuran is -- I think that's a three-fold difference. That's a log scale right there (Indicating). I'm pretty sure aldicarb and carbofuran in the brain is about three-fold difference.

So I just wanted to make sure the panel had the most recent information.

DR. HEERINGA: Dr. Lowit, that particular plot is -- is that in a document that we have received?

DR. LOWIT: It's not on a document you've received. We certainly can make copies.

DR. HEERINGA: That would be great.

DR. LOWIT: It is publically available in the -- in the risk assessment.

DR. HEERINGA: Both the

DR. LOWIT: The accumulative assessment.

DR. HEERINGA: Both that and the half-life chart I think we could use.

DR. LOWIT: Definitely.

DR. JONES: I'm responding to -- first, I'm Dave Jones of EFED. I'm responding to the question about drinking water treatment and environmental degradation rates. Yesterday, I indicated that it is driven by hydrolysis and pH dependent. At pH 5, we have no evidence of degradation. It's a thirty day study, so take that into account. At pH 7, it's twenty-one days. And at pH 9, it's fifteen hours. That's the twenty-five degrees. It's faster at higher temperatures and slower at lower temperatures, and we do have some data on that.

We have an aerobic slow metabolism study. We had two of them done in the same soil, and the second one was limed to raise the pH. It was three hundred and twenty-one days at the lower pH, and a hundred and twenty-nine days when it was raised above seven. That study is a little hard to interpret because there was a great deal of un-extractable residue in the study and it's hard to say whether that was truly un-extractable or just poorly extracted. There was -- degrade, three hydroxy carbofuran. We do occasionally see that in water resources.

In -- if carbofuran is on a surface or in clear shallow waters it does degrade by photolysis with about a six day half-life. But that would only be operative in certain environments where a lot of light can get to it.

Carbofuran is not bound tightly. The median K/F is point 7. So it's below one most of the time. The range is -- the measurements we had goes from point one to thirty point three. So this is a pretty mobile compound.

One comment to add on the drinking water treatment. The water sources we are most concern about, which are private rural wells, tend not to have a whole lot of treatment done to them. So, the question about treating it mostly relates to community water supplies that are both surface and ground water.

DR. HEERINGA: Thank you very much.

In summary -- I don't -- Mr. Jones, with regard to community water systems and the original I read, I didn't see much concern there in terms of community water systems levels, sub-part per billion. Is that correct or is that

DR. JONES: For ground water, our concern is mainly with the private rural wells and that certain environment -- shallow, a lot of sandy soil,

organic carbon acid water.

DR. HEERINGA: Right. Okay.

Are there additional clarifications from yesterday from the EPA Scientific staff?

Well, let me open the floor to questions -- clarification from the panel. Dr. Bunge?

DR. BUNGE: Thank you. Annette Bunge.

Just a couple points of clarification, and I apologize. As you can imagine, we've been overwhelmed both by information and piles of papers. So there will probably be really simple things that we've just lost, or I've just lost. So just a point of clarification -- on the red blood cell, cholinesterase measurements by FMC, they use the modified Elmans Assay in the two dermal studies, and I thought from yesterday's presentation in the second oral study, but I didn't catch what assay was used in the first oral study?

DR. LOWIT: Yes, in the first FMC comparative study, they used the modified Elmans, but it was performed at a different laboratory.

DR. BUNGE: Okay. I see.

DR. LOWIT: So the dermal study for carbofuran and the second FMC CCA study were performed at the same laboratory.

DR. BUNGE: Okay. Thank you.

Now, I'd like to ask just a few questions then about the dermal-tox studies, and especially directed towards the decision to not use the results in the risk assessment.

As I understood it -- okay, first of all point of clarification. The -- I see cholinesterase measurements were done -- it says one hour post exposure, and just to be sure I understand when that occurs relative, does that mean one hour after the six hour exposure on the last day?

DR. LOWIT: Yes, that's correct. One hour post exposure, so actually, seven hours from the beginning of exposure. One after the six hours.

DR. BUNGE: But it's the exposure on the last day?

DR. LOWIT: Correct.

DR. BUNGE: Okay. Now

DR. LOWIT: Just to be clear. As this is a carbamate and recovery is rapid, the fact that it was a twenty-one day study, and it was the last day, is less important then the hours and the minutes.

DR. BUNGE: I appreciate that. I understand that.

And of course there's two studies. There's the seven day study also. And so it would be on the

last day of the seventh day study.

Now, in my understanding of the decision making for not using the dermal studies in the risk assessment, the first was that the red blood cell data were considered unreliable; correct?

DR. LOWIT: Because there was concerns from the CCA study with the same protocol, the red blood cell data, there was no dose response. So, correct.

DR. BUNGE: Right.

But the brain data were considered adequate?

DR. LOWIT: In the CCA study; correct.

DR. BUNGE: Okay.

DR. LOWIT: But not the dermal.

DR. BUNGE: No, I'm talking about the dermal -- just the data themselves, not back to the time course, which I'm going to address in my next question.

DR. LOWIT: Okay.

DR. BUNGE: But in the list of reasons why the dermal-tox study was not included -- or not used in the risk assessment, the list said that the red blood cell data were considered unreliable. I assume then -- though -- that the brain data -- the time course issues aside for the moment, were considered

adequate or apparently reliable?

DR. LOWIT: For that compartment.

DR. LICCIONE: Yes, we had -- hi, my name is John Liccione from ATB. We had like the CCA study -- more confidence in the brain cholinsterase measurements.

DR. BUNGE: Okay. So there's not a question of reliability on the data from the brain, it's now the time course issue that's the critical one? Is that correct in the decision making?

DR. LICCIONE: Yes.

DR. BUNGE: Okay.

DR. LOWIT: There are two points here I just want to make sure that you don't mix them up. One is the reliability of the conduct of the study itself. And then the second issue is the usability of that for point of departure. So make sure in your mind that you're separating that.

DR. BUNGE: I understand that.

Okay. So, it seems to me that the really crux-point then in the decision making on whether or not to use the dermal study in the risk assessment relies really on the time course; is that right?

DR. LICCIONE: Well, there's two issues. One is the time course, but also, the RBC that we --

it's a method problem. All those factors that were considered. So the -- of the oral studies are showing the RBC to be more sensitive. So there's two levels. One is that the RBC is just simply unreliable, and that's the more sensitive compartment. And then you have the issue about the time to course. That would be relevant to the brain, but also would be relevant to the RBC, if they did RBC properly. We would still have to make sure you're -- in the dermal study that you have the right kind of peak measurements and things like that.

DR. BUNGE: Let me clarify it then. So, the fact that -- so, you've decided that the red blood cell assay is the key one. And so if that is deemed unreliable then the other issues aside is still -- the fact that the brain data seemed to be consistent and has a dose response and so forth, you wouldn't use it even if the time course wasn't a separate issue?

DR. LICCIONE: Right. We would -- we would want

DR. BUNGE: I mean, you made the decision that the red blood cell is the assay that matters here?

DR. LICCIONE: Right.

DR. BUNGE: Okay.

DR. LICCIONE: That's the most important.

DR. BUNGE: Now, if I can, then, because I want to be sure that I understand better the rational for the time course data. And I think that could be best explained is if you could explain what data you would have needed to make it possible to use the dermal-tox study -- you believe? What was missing -- just saying time course is not helpful. We need to know a little more specifics about what sort of time course information you required?

DR. LOWIT: Typically -- specifically, from the carbamates, we like to have -- you say time course -- but measurements within that peak inhibition and recovery phrase -- like I showed yesterday. So, for other dermal studies for carbamates, we have measurements taken, say for example, at fifteen minutes, thirty minutes, you know, every fifteen minutes for the first, at least, hour to two hours.

DR. BUNGE: Can you identify whether you mean post exposure?

DR. LOWIT: Yes, post exposure.

DR. BUNGE: Or how about the length of the exposure?

DR. LOWIT: Six hours. Six hours of

exposure. So, like it was done here. But then we would need the fifteen minute post exposure measurements so that we can define the peak inhibition and the recovery phrase.

So, like I said yesterday, for this dermal study, we have a snap-shot in time. And we don't know where that fits. So we don't know if these inhibition data that we have now for brain is the peak or if we're coming back off the peak, in order to be protective.

DR. BUNGE: Can I ask you a question then about the six hours? Why not eight, why not ten, why not four or two, is there a reason for the six?

DR. LICCIONE: Well, the typical -- well, the guideline studies requires -- asks for six hour exposure -- just by convention. That's been considered usually relevant for an eight hour exposure roughly. They could do it longer if they wanted to. But the guideline specifies six.

DR. BUNGE: Right. I didn't know that. I'm more familiar with the dermal absorption guidelines then the dermal-tox guidelines. Thank you. Those are my questions.

DR. HEERINGA: Dr. Brimijoin?

DR. BRIMIJOIN: This is a real quick follow-up.

Do the guidelines also specify that you want the fifteen minutes, the thirty minuets, the one hour, etcetera?

DR. LICCIONE: The guidelines don't specify that specifically. However, in the dermal-tox guidelines do say that you should consider formal pharmacal-kinetics and what you know about the information about the chemical. So knowing that this is a rapid reversible inhibitor and that reactivates, and that we see this to be an issue with the oral studies, why shouldn't it be pertinent to the dermal, as well. Because the dermal pharmacal-kinetics might be actually a little more complicated, because some evidence that we have on the dermal absorption although be it limited on carbofuran is that it follows more the -- it doesn't follow fixed law diffusion. So it could be a little more complicated then the oral absorption, which is just rapid.

So that -- that should be included in the assessment of the Cholinesterase inhibition in dermal if you really want to get down to the bottom-line where you're looking at the time course and being able to reliably measure the cholinesterase inhibition.

DR. HEERINGA: Just a reminder to all of the panelists and the speakers. State your name for

the record so we could that on the transcript. No problem though.

Dr. Brimijoin?

DR. BRIMIJOIN: That was essentially my question, and I think you answered it. And, in fact, it wasn't in the guideline that they must do this. It was a rather vague understanding and

DR. LICCIONE: Correct. But it's open to -- so that anyone that really wants to do it can do good science.

DR. LOWIT: The -- I have one comment about the guideline issue. The guidelines are meant to be flexible. They're not meant to be recipes to follow. Carbamate studies tend to come in with time course. FMC did time course with the oral studies. It would make sense to do some sort of time course.

DR. HEERINGA: Dr. Bailey and Dr. Macdonald.

DR. BAILEY: Good morning. I wondered if I could see slide number -- it's on page 16, or slide 16?

(WHEREUPON, there was no response.)

DR. BAILEY: Last night when we left we were looking at some graphs.

DR. HEERINGA: Of what?

DR. BAILEY: Oh, yes, right here (Indicating).

DR. LOWIT: For which study?

DR. BAILEY: That was -- the PMD 17, the carbofuran, and it was just before the carbofuran acute database. Okay. Thank you.

These are two statistical questions. I believe this is a plat of means here; is that correct? And the dots represent means?

DR. REAVES: Yes, that's correct.

DR. BAILEY: Okay. And can you tell me how many number were used to compute those means?

DR. MOSER: Yes. Good morning, Ginger Moser.

We had, in that study, ten animals in each dose group. And the motor activity and both cholinesterase were measured in the same animals. So it was ten animals per dose.

DR. BAILEY: Thank you.

DR. MOSER: And those are standard errors shown.

DR. BAILEY: And I'm curious why the lengths of the bars are so different as you go around the different means?

DR. MOSER: I'm assuming you're talking

about the motor activity data. Because that's really the one where the variability changes so much of the doses?

DR. BAILEY: Yes, I am. But this is characteristic of a lot -- almost all of the graphs that I've seen.

DR. MOSER: What tends to happen is when you get to the higher doses, for instance with the motor activity, pretty much all the animals are down around zero and so you do end-up having less variability when you get at the lower doses or in the controls. You can look at the controlled values, even though that's a hundred percent, that's the average of the, you know, the main control, and you can see there that the motor activity in the PMD 17 animals are much more variable and that rank -- that variability is the same in the lowest dose animal -- of animals. But then as you go up in dose, and you start having the effect of the chemical, they become more consistent as they get down to zero, which of course you can't get below zero.

DR. BAILEY: Yes, and that's a -- I understand that. That's a very good answer. But then on slide number 12 -- then I see that -- that doesn't seem to hold -- that was -- the slide I'm referring to

is carbofuran acute database oral -- the slide just before that section?

It's the time course data?

DR. REAVES: For which? The FMC study? Or the EPA study? Or?

DR. BAILEY: I'm sorry. I've lost track from where we were yesterday afternoon. Let -- the one in the middle would be fine. So some of these -- now, here again -- they're quite different lengths. It's indicating the variability is -- of the estimation of those means is quite different. No matter -- sort of throughout the range and during the time course. I've seen this in many of your graphs, and I'm just curious as to why those -- there's so much variability?

DR. MOSER: I think one of the answers could be provided by FMC, but I know that as you saw in the tables with what they call the DNRs and the cases where they had to throw out the data completely. Sometimes the sample size would go from ten to maybe only four, and I believe those are still standard errors. And so it's heavily dependent on the sample size. So, it -- I don't -- those are my data of course, but I know that there were many cases where some of those groups only had two to three animals, and other groups for some reason didn't have as many data

points thrown out and they may have eight, nine or ten animal, and so of course the standard error is going to be much lower. I believe that to be the case to at least contribute to that -- those differences in the variability.

DR. REAVES: And maybe later on today, FMC could answer more questions around their specific data.

DR. HEERINGA: I think that's fair to assume. And I think an explanation of not only the natural variability in the original measurements, but the changes in sample sizes resulted the DNRs and the development.

DR. BAILEY: Right. Though our concern is does this just -- does this represent -- my question about reliability in the data or is this, in fact, reflect an underlying biological process that's going on?

The second question I had -- back to the first draft we were looking at and the mark on the scale lines was in percent change, and I'm concerned about using percent as the scale -- as the scale, because you could go -- a ten percent change could be one hundred on the basis of a thousand if the units are in the thousands. You'd take -- ten percent of that

would be a hundred, but if the basic levels are at ten, the change would be only one unit. And isn't the actual units that it's measured in of interest to biologists? Or is the percent change around a thousand or is it around units of, you know, ten units or something? That was my second question about -- aren't we interested in terms of the actual units, as well as the percent change?

Thank you.

DR. MOSER: We are interested in both. And because of that, the statistical analysis are always conducted on the actual data -- the raw values. The reason we put everything as a percent control for a lot -- for these comparative graphs, was because there is such difference in the control values. For instance, the brain Cholinsterase is, you know, the numbers that we get for the brain Cholinsterase is about ten-fold that what we get for the red blood cells. So to put the actual raw values on the same graph it would look, you know, you would have to change the scale and it would be very difficult to compare.

But the statistical analysis are always conducted on the raw values.

DR. BAILEY: One last comment. Then maybe you could use both axis -- on the right vertical

axis, you could put down there what their scale is and then people could see both what the actual units are.

DR. MOSER: Well, that would be possible --

DR. BAILEY: Thank you.

DR. MOSER: But would be difficult with the motor activity as well, but if you care to see those data, you know, the raw data at some point, we could provide it. But there are differences obviously in the control values. Especially -- and also across ages. The younger animals have much less brain Cholinsterase activity then the adults do.

DR. HEERINGA: Dr. Setzer?

DR. SETZER: Yeah, this is what -- from the U.S. EPA If I could expand on that just a little bit First of all, when we're trying to put different say data from different age groups or whatever on the same graphs, what Ginger just said is exactly right. You really want to represent that as percentage control just so you can see things because the background levels change a lot.

Secondly, in terms of the biological effect or the significance of the biological effect, since this is -- since this is an enzyme and it sort of -- it tends to act sort of multiplicatively. So what matters

is relative changes from backgrounds. So it really doesn't matter what -- I mean, if you were going to actually try to build a mathematical model of recovery of nerve function, you certainly would want to know absolute units. But if you want -- but if you're trying to get an idea of the relative effect, what you really care about is the fractional change. So one percent -- one percent is different from ten percent, but the actual units you use aren't so important.

When we do the analysis for these data regardless of how we're doing them, we always work on the original scales and -- because obviously sort of re-scaling like that can be risky. But -- and if you're not careful can introduce correlations you've got to then deal with in the analysis. But for representational purposes, we use percent change, and that's actually the right way to think about it mechanistically as well.

DR. HEERINGA: Thank you, Dr. Setzer. Dr. Macdonald?

DR. MACDONALD: Yesterday, we saw a very useful table entitled EPA and FMC Net Analysis Estimates for Juvenile and Adult Rats. Page 25. Next time, it would help if you would numbered the -- numbered the individual slides. It was just before --

the end of section three.

Yeah, I think this is very useful. And I think this is very important for our discussion of charge question one in human health and I would find it really useful if I could have a list showing the source of each of those numbers. Because I know they've come from various -- various sources. But it would really help if I could find out where each one came in the background material so we can have a discussion of that when we get to charge question one.

DR. LOWIT: Can I ask a clarification on what you mean by source?

MR. MACDONALD: Sure.

DR. LOWIT: Do you mean which of the mountain of papers we have?

MR. MACDONALD: Yeah.

DR. LOWIT: Those numbers came from -- or the source being which data -- which studies --

MR. MACDONALD: No, I --

DR. LOWIT: -- including the numbers?

MR. MACDONALD: Where can I find them in the pile of paper?

DR. LOWIT: Okay.

MR. MACDONALD: You see at the moment, being a distrustful statistician, I won't even -- I'm

not even willing to assume there aren't typos on that table. So, as well as just making sure that the numbers got transcribed correctly, I'd like to know where each one came from, and then, if I could find it in the background material, I can get some idea of the reliability of each of those numbers, which makes the comparison easer to do.

DR. LOWIT: I think we know roughly where they come from, but I can't quote you the titles right this second. At the break, we'll talk about some titles.

MR. MACDONALD: If we can have this -- if I could see this before we have to prepare for charge question one and Human Health that would be really useful.

DR. HEERINGA: Dr. Lowit, is that something that you can do I guess in a reasonable period of time?

DR. LOWIT: It should only take a few -- I hope it should only take a few minutes, but there's a mountain of stuff there. I'm pretty sure it will only take a few minutes.

DR. HEERINGA: It certainly is a reasonable request.

DR. LOWIT: Very much so.

DR. HEERINGA: And I think that's -- given the amount of material I think certainly the comparative tables are very useful, but to have this side by side and then others the opportunity to actually go to those original sources and make sure that he understands.

DR. LOWIT: As a point -- just to make sure that we give you what you want, Dr. Macdonald and this may be for the whole panel -- because you each come to the table with a different skill set. Are you just interested in the -- let's see -- the code and the stats behind the numbers? Or you're interested more of the summary information and that sort of thing? Because they may be two different places.

DR. GRUE: This is Dr. Grue. I'm kind of interjecting because he can't help it.

DR. LOWIT: I'm thinking that you want something different than he does.

DR. GRUE: I think these tables that you're showing here are very nice for a talk for sort of presentation of data -- for leading an audience through your thinking process. I think we're going to be asked to get at the nitty-gritty, and I think you should treat these tables the way you would do if you were submitting this for a peer review publication.

And, in such a case, a table would come with a detailed legend that would indicate where the numbers come from, which study, etcetera. I think that would help Dr. Macdonald and the rest of us.

DR. LOWIT: Okay. If you want something like that it will take longer than the break. But certainly by the time -- certainly -- we can probably do it this evening or maybe first thing in the morning.

DR. HEERINGA: Dr. Macdonald?

DR. MACDONALD: Yeah, the other picture, I'd like a little bit more explanation of, which I can't locate it in mine. It was Dr. Setzer's work on giving -- you had a grey band around the fitted line indicating the uncertainty in the extrapolation. And it would be good if you could give us a little more technical detail on how you did that calculation. It would save us having to do it.

Yes, that one. Yeah, that's very pretty. Thank you.

DR. SETZER: I'll see if I can submit it somewhere -- okay, let me remember this. The issue -- okay, what we have here are predictions of inhibition based on the dose response model in the PND 11 data set in red blood cell and in brain. So we have two

different dose response models predicting brain activity -- from those you derive inhibition. The -- so the solid line through the middle is just -- is just the prediction based on the maximum likelihood of approximate maximum likelihood estimates for those -- for the parameters for those models.

The little cloud on either side -- the intent here was to sort of get an indication of the relative -- the relative uncertainty and estimates of BND 10 and BND 50 on these curves. So the way the clouds were generated were by drawing a sample of parameter estimates with multi-variant normal distribution with mean and covariance matrix derived from the maximum likelihood affixed to the data. Since I didn't actually calculate Cholinesterase of that distribution, that simply two draws from that distribution. Again, it wasn't intended to be quantitative, but suggested. So it's two hundred draws from those distributions, but for the red blood cells is the gray and the brain is the light blue. I should say Carolina blue, I guess.

DR. HEERINGA: Yes, Dr. Lu?

DR. LU: Just quick question. Could you comment on the use of six percent dermal absorption versus 8.8 percent as actually concluding the paper you cite in the document?

The six percent dermal absorption reverses 8.8 --

DR. LOWIT: We're bringing someone else to the table.

DR. HEERINGA: Make sure you identify yourself.

DR. LICCIONE: John Liccione, oh, pardon me, John Liccione from HEV.

Of the six percent from dermal absorption -- what's your question?

DR. LU: Because you refer to a paper that published earlier

DR. LICCIONE: Right.

DR. LU: -- which did an animal study on dermal absorption. And the conclusion in the paper, as I remember, I read through is that it was about twelve percent for the juvenile rat and about eight point eight percent for the adult rat -- the absorptions, so in the article I couldn't find six percent anywhere.

DR. LICCIONE: Okay. I could show you -- in fact, I've got the paper her and I can actually show you the actual chart. It's one of the tables where they show the six percent actually goes with the 24 hour measurement. Because there was no eight hour or ten hour measurement that we would use for work or

risk. So it's in the table and it was the one -- where they looked at one dose for a certain amount of time. And the absorption is greater in younger rats as you mention. However, for work or risk, we usually use the adult number. But I could go get the

DR. HEERINGA: May I suggest that you just have a copy made to provide to him.

DR. LU: Yeah, the copy is actually on the cd.

DR. LICCIONE: Right. I could actually, if you'd like just show you the exact

DR. LU: Okay. Sure. That would be great.

DR. LICCIONE: I'd be more than grateful.

DR. HEERINGA: Dr. Bunge?

DR. BUNGE: So just to clarify, the six percent number was from the adult rat?

DR. LICCIONE: Exactly.

DR. BUNGE: After a twenty-four hour exposure?

DR. LICCIONE: Right. We did not have an eight to ten -- ten hour exposure, which we usually use for adult work or risk. Because we typically

DR. BUNGE: Right. I understand that.

But on the other hand a dermal-tox study is a six hour study; is that right?

DR. LICCIONE: That's correct.

DR. BUNGE: Okay. You do have a six hour dermal absorption number in that paper. Was there a reason to not use the six hour number since you would have normally used a six hour dermal-tox results if you'd had the time course data network to make it feel comfortable in your risk assessment?

DR. LICCIONE: I'm going to turn it over to the author of the actual study -- PV could explain more.

DR. HEERINGA: Please introduce yourself.

DR. PRAKASHCHANDRA: P. V. Shab, USEPA. I think the reason the six hours that I did not use is that in this study, the skin bound residue couldn't actually remaining on the skin was considered as an actual dose. Typically, the EPA guideline requires six hours exposure, washing and then we follow it through forty-eight hours, seventy-two hours depending on that. And look at the activity in the urinary excretions. That will help us in deciding whether the skin bound residue is acerbic, acerbic or not. In this study, the data did not -- the skin was not washed. The skin

bound residue was considered as an incidental. So to be on the conservative side twenty four hours later were used -- which is six percent in the adult.

DR. BUNGE: If I can follow up, I have further -- at least one further question. If I recall the paper correctly, it says that in six hours, seventy-five percent of the absorbed dose had been eliminated in urine. And, so, you've -- it seems as though the dose -- we're assuming the six percent dose that was observed over those twenty-four hours was all absorbed as one bolus when we do the risk assessment. Whereas we know from your data in the paper that in that same six -- in a six hour period already, you didn't -- you may have quoted the other number for the twenty-four hour, but I don't remember it, but already only 25 percent of that bolus is even still in the body.

I don't know what how that would exactly affect the risk assessment yet, because I haven't thought it through that whole process, but would you like to comment on the fact that in the risk assessment calculation, we're using this twenty-four absorption number -- twenty-four hour absorption number basically assuming it's all introducing into the body or the bolus even though we know that most of it, at least

three quarters of it, probably isn't there any longer?

DR. PRAKASHCHANDRA: The only thing the data indicates that at six hours in an adult there was two percent absorption. And in twenty-four hours we had five point seven. So it looks like it's not a bolus because we have a continued absorption appearing in that.

DR. BUNGE: But in the risk assessment, basically it's being assumed to be introduced as a bolus. We understand that it's not, and your data shows that it's not, but in the risk assessment the assumption is six percent absorption, and then it's -- that number is used based upon the oral, which is assumed to be a hundred percent absorbed; correct?

DR. PRAKASHCHANDRA: Correct.

DR. HEERINGA: Thank you, Dr. Shab.

Other questions of clarification? Again, we can return to some of this later.

Dr, Bunge, are you -- Dr. Brimijoin, I think -- no, no. I'm turning to you because I think you're probably are -- have questions of most of everybody here. Are you satisfied at this point? And again, if anything else comes up, let us know, we'll ask it.

Yes, Dr. Schlenk? Oh, that's Dr. Bunge.

DR. BUNGE: Having said I didn't have

anymore questions. Annette Bunge. I do have one last one. I think it was the very last slide where you talk about the dermal exposure for workers, and this is in the risk assessment. And going from the 2006 risk assessment to the 2007/08 risk assessment, and the number that you're using now increases by two-fold, you may have said why that was, but I missed it?

DR. REAVES: Right. In the 2006 -- this is Melissa Reaves. In the 2006 risk assessment, we only had the first FMC study to base our oral end point for the dermal scenario. The same for the oral end point from the CCA study. However, in 2007, we received all the other oral data; the EPA data, the second FMC/CCA study, and so new BMD analysis was rerun with all the data, and the difference in the BMDs then is two-fold.

DR. BUNGE: Okay. So, it's just the difference in the oral

DR. REAVES: Right.

DR. BUNGE: -- calculation of the BMD?

DR. REAVES: Right. So there's more data in the point oh two BMDL.

DR. HEERINGA: Dr. Schlenk?

DR. SCHLENK: Dan Schlenk. I just wanted to follow-up on a question that was asked

yesterday before everyone left. I forget who -- maybe it was Jim or somebody. But there was a question that was asked -- the correlation between the RBC inhibition of Cholinesterase with some of the motor activity, or was there actually some Cholinesterase measurements done in diaphragm or in the neuromuscular tissues, and I think there was somebody who said that there was a correlation somewhere. I went to the McDaniel and Padia papers -- and I didn't see -- the only correlation I saw was with motor activity. I didn't see any correlation with sort of muscular enzyme activity.

I was wondering has that been done? And just so that I understand this, it seems to me -- because it's very confusing because of all the different age groups I think. But in that paper, at least the last line says that brain Cholinesterase activities -- let's see if I get this right -- says, these current data support the use of brain Cholinesterase activity of all RBC when evaluating neuro-toxicity for these chemicals. Now, I assume that that's in the adult rats.

And then when I was looking at the presentation yesterday, you have a presentation that shows where the PMD 11 rats that motor activity was not evaluated. So -- but brain and RBC data was -- or

Cholinesterase was. So, my question is, are you extrapolating -- well, first of all, is there any measurement of toxicity in the PMD 11 animals? And has that measured toxicity been compared to the indicator of exposure, which is RBC Cholinesterase? I guess that's my question -- in PMD 11 animals?

DR. MOSER: This is Ginger Moser. That's a great topic, and I could spend all morning talking about it. But in the McDaniel paper, as you say, we did the regression analysis with the brain Cholinesterase and the motor activity, which is what's up there right now. We actually did look at the same regression with the red blood cell data, and the correlation coefficient was a little bit lower. Now, whether that was because of the higher variability in the red blood cell data or is it just that it's less correlated with motor activity -- it could be either one -- you can't tease that out.

Some of the statements of the -- I had made about corresponding to other types of motor effects or other types of toxicity effects comes from some older data that we published at least ten years ago. Mostly with organic phosphates, and in particular, chlorpyrophos. And in one paper we did actually look at a lot of different kinds of in points, including

salivation and lacrimation some of the ergonomic end points some of the other motor end points, as well as tremors and fasciculations, and we did aggression analysis with many different Cholinesterase measures, including diaphragm, and including muscle, and different areas of the brain, as well as plasma and blood, and whole blood and red blood cell. And basically, the bottom line from that was that the -- there was no one -- one tissue Cholinesterase inhibition that correlated much -- much better than anything else. And because the Cholinesterase inhibition is all kind of correlated within the same animal anyway, I think that's part of the reason why. And that was all on adults.

Now, when you switch to the younger animals, PMD 17, we have used a lot because of the fact that at PMD 17 the animals are mature enough to start showing motor responses and that sort of thing. At eleven days of age, they don't move. They're very little. The nervous systems are very immature. And, in fact, it's somewhat difficult to even see signs of toxicity in the PMD 11 pups because, for instance, tremors is one that I'm always a little skeptical about. If you've ever watched a PMD 11 pup, when it tries to take a step it will kind of shiver, and some people call that tremors.

It's not tremors. It's, you know, just something that they're doing. It's the way they're moving. They're not very -- they don't have fine movement yet. The nervous system is not myelinating at all. And, so, you can't look at that. You can't look at motor activity. Their cholinergic system is not well developed either. So some of the cholinergic responses are sometimes not there. So it's much more difficult to see clear signs of toxicity until you get to the really high does where you're getting out right convulsions and death and we don't go that high. We don't want to.

So that's why in the PMD 11s, we have just limited our analysis to the Cholinesterase inhibition, and I think that that's why when other laboratories do try to do some kinds of observations on those animals it's variable -- a lot of it's going to depend on the technician who's doing the observations. But maybe they don't even understand the very limited repertoire of the PMD 11 animal. So, therefore, we don't have much of the toxicity data. We've never tried to do any analysis of regression or correlations with Cholinesterase inhibition in those animals.

I think that answers all your questions.

DR. SCHLENK: I think so. I just -- just to make sure that -- so you're basically

extrapolating from the PMD 17 to the PMD 11 as far as the toxicity's concerned? Because you only have motor activity in the 17 animals, and you're assuming then that the toxicity would be the same in the 11 animals. Is that -- would that be accurate?

DR. MOSER: We're assuming that because we see changes in the adults -- in a lot of different affects we see changes in the PMD 17 animals at low dose -- you know, variable low levels Cholinesterase inhibition -- that there is some toxicity going on in the PMD 11 that we can't observe. But there is so many other things going on in that PMD 11 animal that you need to predict. You still got the whole nervous system is being developed, and we know that Cholinesterase has a major role on the development of the nervous system that we're not going to get into developmental neuro-tox at this point. But, I mean, the assumption is that you need to protect against the very low levels of Cholinesterase inhibition in the young just like you do in the older animals.

DR. SCHLENK: Okay.

DR. LOWIT: Can I answer -- add one more clarification.

DR. HEERINGA: Yeah. I want to move things along here at this point.

DR. LOWIT: Sure.

DR. HEERINGA: Because I want to make sure -- we're pressing on the point where we may not even get public comment in. Dr. Lowit?

DR. LOWIT: I'm glad you're the chair. We need to keep moving.

There's a context saying to the McDaniel paper I just don't want to lose. That the McDaniel and the Padia papers were developed in part of accumulative to look at the class as a whole. But certainly our experience has shown us that where classes have patterns -- that each individual chemical has it's own unique properties and unique characteristics. So, take the conclusions on those papers with the caveat that each chemical has it's own properties.

DR. SCHLENK: Yeah. Actually, I looked at the table that actually shows the piercing coefficients for each chemical and actually that's what I was basing my comments on is that table.

DR. HEERINGA: Dr. McCarty?

DR. MCCARTY: John McCarty. Just a quick follow-up about the correlation here, and you've shown some of the correlations, and you've also shown Cholinesterase recovery in the rats. Is the same --

I'm assuming these are based on point estimates of maximum inhibition. Is the same trend going to be evident if we look at recovery? Will recovery of behavior follow a similar time course as the recovery in Cholinesterase activity based on this figure?

DR. MOSER: This is Ginger Moser, and that's a very tricky question. Because it has been shown that recovery of the behavioral of functional deficits happens actually a bit more quickly then the Cholinesterase recovery. Mostly the POPs because the Cholinesterase inhibition lasts for so much longer. But somewhat with the carbamates as well, and there are other transient things that go on at the nervous system synapse that are producing that recovery at a quicker level.

DR. HEERINGA: Dr. Lowit, any last

DR. LOWIT: Yes, we're going to make -- Bill Jordan, who's now sitting here next to me, wants to provide a little bit of context around -- to help the panel, before you cut us off.

DR. HEERINGA: Okay. And there will be opportunities to return to this, because I think you have summaries before the charge questions. Dr. Jordan?

DR. JORDAN: Thank you, Dr. Heeringa.

I understand that earlier in the discussion, a question arose regarding the 21-day dermal toxicity study in rodents, and some questions arose about the basis for rejecting -- EPA's decision to reject that study as a starting point for our analysis.

Our decision is grounded on concerns about the methodology used in that study, which have been explained. And I want to attempt to recover -- cover that ground again. But another question arose about whether it is appropriate to look at the human toxicity -- human dermal toxicity study with carbofuran in order to make some sense out of the 21-day dermal toxicity study in rodents.

EPA has in place, as some of you will know, a regulation regarding the consideration of human intentional dosing studies. And we have evaluated the human dermal toxicity study with carbofuran and determined that we are not going to rely on it in our decision making. That judgment, therefore, means that we -- EPA -- have not cited that as part of our -- part of the factors that we consider in evaluating the 21-day dermal study in rodents.

However, if the SAP wishes to look at the human study, we don't regard under our regulation that EPA is relying on it. And if you think it is relevant

to evaluate the -- compare, for example, the levels in human dermal toxicity study that elicited clinical signs with levels in the 21-day dermal study that were tested that would be permissible under our regulation.

DR. HEERINGA: Thank you, very much.

I guess, Dr. Bunge is taking notes.

DR. BUNGE: Just one clarification. Under the Federal Advisory Committee Act, the two separate functions of the two advisory committees are distinct, and one doesn't revisit in a second federal advisory committee of another advisory committee's recommendations, so we're not going to discuss that study at all during this meeting.

The human studies review board has already made their decision. The agency's made their recommendations, and those issues are not on the table.

DR. HEERINGA: Okay. At this point, what I would like to do -- is we are about to enter the period of public comment. And the period of public comment -- if you just do the simple addition -- as I've done -- on the agenda, which stretched for six hours without any questions -- that obviously the likelihood that there will be no questions is very small. Not impossible, but probably small. So we'll move right now to -- I want to call just a twelve

minute break to give people a chance to stretch and -- everything's going to be shortened up. We're on march time today. So, a twelve minute break. Let's meet back here at 10:00 a.m., and we'll continue with a period of public comments.

(WHEREUPON Session A was concluded and a break was taken.)

DR. HEERINGA: Okay, welcome back, everybody, to the continuation of the morning session from the second day of our meeting of the FIFRA Science Advisory Panel on Scientific Issues Associated with the Agency's Proposed Action under FIFRA 6(b) of a Notice of Intent to Cancel carbofuran.

At this point in time, we are at the period of public comment. The period of public comment will include a number of contributions from people who have registered to speak with the Designated Federal Official, Sharlene Matten. Presentations will be given in the order established by Dr. Matten which, I believe, is the order of initial requests to speak.

We begin with a series of presentations by FMC that we expect to last about three and a half hours. I think that's in presentation time, and I suspect it will go longer than that with questions, followed in order by other registered public

commenters.

If anyone is in the audience and has not had the opportunity to register as a public commenter, if you would like five minutes...and that's sort of the late arrival time limit...please see Dr. Matten during the break or at noon hour. Otherwise, I think we're set to being.

At this point in the process, I'd like to open it up by turning to Dr. John Cummings of FMC Corporation who will do introduction and overview on new carbofuran use patterns and use production. Dr. Cummings?

DR. CUMMINGS: Okay, thank you, Dr. Heeringa, and thank you to the panel for allowing us the time on the agenda, because this is a very important action. And good morning.

What I'd like to start with is...is this morning is to present a brief presentation prior to the scientific presentations to set the stage for our...for our comments and our...for our scientific position.

I would like to echo a couple of the EPA's opening comments from yesterday and would agree with their...their comments. One, obviously, is this is a very important SAP panel hearing and, to a degree, historic. I think I'd use...I heard that word

yesterday.

And the other comment I would like to echo from the EPA's opening remarks yesterday is that certainly, the SAP should consider all relevant and currently available data in determining the nature and magnitude of risk that carbofuran presents to public health and the environment.

Also, as you heard yesterday, FMC, the registrant, has submitted significant amount of new...new data, new information that refines the risk assessments, and following the scientific presentations, hopefully, you will conclude, as we believe, strongly supports the continued registration of carbofuran in the United States. Said another way, that it meets...carbofuran meets the FIFRA and FQPA scientific standards for registration and re-registration.

So, the format of the presentations today, as Dr. Heeringa has mentioned, is that I'll be providing a...an introduction which primarily focuses on two pieces. One is on the use of carbofuran, how much is used and where it is used and the relevance for risk assessment. And then, also, to focus in on registrant-initiated mitigation measures that have occurred over the past several years to mitigate potential concerns

as well as to detail, provide a little bit of detail, on the proposed label as we've...as we've briefly discussed over the last day to provide some context for that as well.

Following the introduction, I think it probably appropriate to pause after that, any clarifying questions if the...if the chair chooses to do so, and then move into the scientific presentations on avian risk, worker risk, human health and dietary risk, as well as water risk, and you'll hear that from a panel of experts which I'll detail in a few moments.

On this slide, really, the key message here is that if you look at the table to the right-hand side of the screen, carbofuran used to be widely used in the late '70s, early '80s very widely on numerous crops. If you look at it, for a typical year in the peak year of sales was around...typ...typical use was 10 million pounds of active ingredient per year. And, again, this was in the late '70s and early '80s.

Primarily due to market forces, the introduction of alternatives and...and...and other elements, this use has declined in 2006 to roughly 6 percent of its peak year sales. So, only 600,000 pounds of active ingredient per year.

This is important, I think, in consideration,

as you heard yesterday from the incident reports and other elements that the Agency presented. We certainly do need to consider this...this limit, very limited use in the relevance of the incident reports, incident reporting, that were pre-1995. Is that information relevant? And...and...and it is our position that that probably should be weighted much less than the most recent data post 1995.

As you see on this slide also, there is a projected sales, and this is projected at about 300,000 pounds, only half of what is currently being used. And this...I'll...I'll spend a little bit more time on this, and this is really what FMC and many of our experts project will be used in the future based on our proposed label changes.

The...and, also as you heard from the Agency yesterday, really, the 99 percent of this...of the use of that 600,000 pounds currently being used is in the flowable or liquid formulation. There is a very small use of granulars, accounting for 2500 pounds, 2,500 pounds of active ingredient per year, and this was arrived at with a...through negotiated settlement with the Agency back in 1991. So, very limited use, and the focus will be on the liquid formulation.

A question may arise from the panel on why is

FMC, the registrant, interested in...in...in retaining carbofuran for 300,000 pounds of active ingredient per year when we used to sell 10 million pounds, and that's a very good question to ask. Really, there's two primary reasons.

One is that we have gotten strong indications from the growers, from the users of our product, that there are essentially five uses that are critical. There are no viable alternatives available out on the marketplace today or in the near horizon. And, certainly, from an economic perspective as the company who sells this product, we see that there is an ec...economic reason to continue that registration.

The other reason is we are firm believers, as members of...responsible members of the agricultural chemical industry, that regulatory decisions should be based on sound scientific principles, and I think that's why we're all here today. And, certainly, as you'll hear throughout the day, our position is that if sound science is used, then carbofuran should be registered, and, certainly, we are willing...we are...we are interested in keeping this product on the market because risks are acceptable. Okay? So, you factor those two pieces in together.

Now, I mentioned the critical uses, and I'm

not going to spend a lot of time on this. However, I think it's important as context.

Benefits assessments, both from a biological and economic perspective, have been provided to the Agency. They have not been provided to the science advisory panel. However, there is extreme economic value for retaining the following uses, that is, use on corn, use on cotton. I'll spend a little bit more time on that. Potato growers have indicated it's critical for use in the Pacific Northwest. Melon growers and sunflower growers have all said there is not a viable alternatives, and there's significant information that's been provided to the Agency to show the economic and biological value of these products...of this product on these uses.

Moving to the scientific part...portion of this discussion, when the interim re-registration eligibility decision came out in 2006, August of 2006, FMC assembled a world class panel of experts in these four areas, avian, worker, acute dietary, and ground and surface water, to advise us to say this is the current risk assessment by the Agency. Assess the scientific validity of their assumptions, recommend are there other studies, data that could be developed to refine this, and are there refinements in the

risk...other refinements in the risk assessment that would be useful in reducing the uncertainty and improving the risk assessments.

As I mentioned previously, also in that time period, experts were assembled to address the benefits of these products as well, working closely with the commodity organizations and the individual growers of these...of...of these commodities.

There have been significant mitigation measures that have been put in place, and I think the...the EPA did highlight some of these yesterday and mentioned that FMC has implemented significant mitigation measures over the years, over the last 20 years, primarily the first...I'm not going to walk through these individually, but the first five bullet points, really, I think the Agency had similar presentation yesterday indicating that FMC has initiated an effort to mitigate any concerns in potential vulnerable areas on risks for carbofuran to reach groundwater and surface water.

And many of these are geographic restrictions, reducing number of application rates, reducing...or, I'm sorry...application rates and numbers of application rates, and the geographic restrictions being focused on vulnerable soils.

Again, these are...these have been implemented. They are on the current label, that is, in the marketplace today.

Shifting to worker exposure, the next to last bullet point on the slide before you, all furidan, carbofuran-containing products, are...liquid products are in state-of-the-art mixing and loading closed systems. You'll hear a lot more about that when our...our panel of experts from work...from the worker risk assessment come up to show that, really, there is minimal exposure to...minimal occupational exposure to the workers.

Also, last but not least, there is an extensive product stewardship program that FMC heads up, including brochures, extensive education programs out for the users of our products. Unfortunately, with the time today, we don't necessarily have a lot of time to cover that, but it is extensive.

Unfortunately, as you look at this list of already implemented programs and...and label changes, a lot of these mitigation measures have not been accounted for in the current EPA assessment that's been...that's before you at this point and really led to overly conservative assump...conclusions from our perspective.

Let me shift now. What I just talked about was the mitigation measures that have been implemented. Let me shift to saying...to...to the major items of the proposed label that has been briefly discussed over the past day.

Essentially, what FMC has proposed is to only retain five uses, those critical uses that I mentioned before, in the current label. That results in the removal of 12 federally registered uses, removal of 13 state registered, what's known as special local need uses, as well as additional prohibitions and restrictions in areas essentially vulnerable to...vulner...in vulnerable water bodies, and I'll detail that in a little bit more in...in...in a future slide.

So, if we look at the uses...and this is just more of a...a graphic representation of what uses are being proposed to be retained. If you look on the right-hand side of the slide, there are those five uses which I touched on before, melons, sunflowers, field corn for post-application only, potatoes in the Pacific Northwest, and the pending cotton use.

And I do want to pause there briefly to just mention some...provide some clarification, because there were...Dr. Bradbury this morning did mention the

cotton use not being registered. I just want to provide some clarification on the situation there.

If you look on the left-hand side of the screen, there is a registered use on cotton at plant. We are proposing to cancel that use. The pending use which EPA petitioned EPA for adding the use of cotton foliar treatments for control of aphids in 1995. That petition has been pending at the Agency since 1995. Okay?

We have included that in our proposed label, and after we submitted the label in early December or mid December of this past year to the Agency, we received notification from the EPA that there was a deficiency in that pending petition. Okay? So, we are...we feel it is our right to include cotton, because it is a pending use. It is not a new submission. We're not proposing to add a new use. It has been pending at the Agency for the past 13 years.

Included on the retained...in the proposed label are also the phase-out crops which the Agency has proposed to phase out over four years as well as, as I mentioned before, the existing granular uses that are very limited, limited to 2500 pounds per year.

Also included on the...included on the proposed label are further limitations, mitigations, to

address potential for surface and groundwater...well, for carbofuran reaching surface and groundwater. These are based on our panel of experts which you'll hear from shortly, looking at the data, identifying vulnerable areas, and we took those recommendations and included those conservative mitigation measures on our proposed label.

They include geographic restrictions, best management practices, and they are consistent in as you look at currently registered labels of other carbamates. These mitigation measures are consistent with other carbamate labels.

The end result, from our perspective and in our conservative risk assessments, that these result in drinking water concentrations estimated below the level of concern by the Agency.

And I'm not going to go through this slide in detail. You have this packet before you. But, essentially, this highlights the restrictions that we are proposing on the label for both...vulnerable both ground and surface water areas. They include prohibited applications within a certain distance, buffers, in specific counties and, in some cases, statewide, to address surface water areas. And from a groundwater perspective, there are statewide

prohibitions, as you can...as you can read from the slide in front of you, as well as applications being prohibited within a certain distance, well setbacks, from all wells in several states and several counties that have been identified by our experts as being potentially vulnerable.

The final mitigation measures in the proposed label address avian concerns, and, again, our avian effects advisory panel, again, which you'll hear much more in detail in a few moments, have done conservative risk assessments on...on the five critical uses as well as alfalfa. And the inclusion for alfalfa is it is a very economically important critical use. However, based on our...our avian effects advisory panel's recommendation, we are proposing to remove alfalfa because of the risk assessment did identify relatively higher risks on gorge feeding waterfowl.

Generally, the remaining uses, the five critical crops, have low or de minimis avian risk, and you'll hear much more in detail from the avian panel shortly.

Let me just introduce...and this is the order of...of presentation. Let me just introduce the...the principal presenters and the members of these various advisory panels.

The first presentation will be on avian effects. Dr. Dwayne Moore and Dr. Keith Solomon will be presenting on behalf of this avian effects advisory panel, made up also of Lou Be...Dr. Lou Best and Larry Brewer and Dr. John Geisy.

Dr. Solomon will be...will be reviewing the additional studies that have been submitted by the Agency...or by...submitted by FMC, and then, Dr. Dwayne Moore will be presenting the Liquid PARAM which was briefly discussed yesterday.

That will be followed by a worker risk presentation. Dr. Jim Lam will be presenting the toxicology studies that will be the dermal tox studies and the...and our position on the appropriate endpoints, and then, Dr. Jeffrey Driver will be presenting the exposure and risk assessment for workers.

The third presentation will be on human health and dietary risk. Again, Dr....Dr. Lam will be presenting on the toxicology point of departure and use of uncertainty factors. Then, Dr. Bob Silken will be presenting a statistical analysis on this data, and finishing off will be Dr. Robert Morris to again do the exposure and risk assessments for dietary.

The final presentation will be from...will be

from our water panel of experts, Dr. Engel, Dr. Fawcett, and Martin Williams, addressing exposure and risk assessments relating to ground and surface water.

So, prior to concluding, I just want to make a couple of conclusion...concluding comments. As you heard from the Agency yesterday, carbofuran has been registered since 1969. FMC has been the sole registrant in the U.S. for 40 years. We take very seriously our responsibility to comply with the law as well as steward our products.

We feel confident, based on real-world experience using carbofuran for the past 40 years, that it can be used safely in the United States and does not pose unreasonable adverse...unreasonable risks or adverse effects to human health and the environment.

As you will see over the next several hours as we present the additional data and the refined risk assessments, we further believe this more strongly supports, in addition to the...the 40 years of use, that carbofuran does meet the FIFRA and FQPA regulatory standard, and its products should not be canceled.

At this point, I'll turn it back to the...Dr. Heeringa.

DR. HEERINGA: Thank you very much, Dr. Cummings. Any quick questions of clarification for Dr.

Cummings? Yes, Dr. Brimijoin?

DR. BRIMIJOIN: So what happens to the projected volume of use if the foliar treatment of cotton is added?

DR. CUMMINGS: That is actually included in those projections, yes.

DR. HEERINGA: Dr. McCarty and then Dr. Montgomery.

DR. MCCARTY: One of the, quote, special...special local needs uses is for Conservation Reserve Program land.

DR. CUMMINGS: Yes.

DR. MCCARTY: I...in the documents, there may be something there, but I haven't seen anything about the extent or frequency that that's permitted. Do you have any comment on when this...when and how often this is used on CRP?

DR. CUMMINGS: I actually don't have that information. I'd ask Dr. Carlson if he has...if he'd like to come forward and address that.

DR. CARLSON: My name is Don Carlson...

DR. HEERINGA: Step up to the microphone, Dr. Carlson.

DR. CARLSON: My name is Don Carlson. I'm with FMC Corporation. My responsibilities are

product development and registrations for carbofuran.

The answer to your question is that there is relatively little use in the Conservation Reserve Program at the current time. The primary use was for control of grasshoppers, and there are other alternatives for that particular use.

DR. HEERINGA: Dr. Montgomery had a question, too.

DR. MONTGOMERY: Hello, this is Cheryl Montgomery. I just have a quick question for you on your slide that deals with amended label reflecting the limited uses of carbofuran.

On the alfalfa, you specified on a slide subsequent to this was being removed because of the potential for gorge feeding of wildlife. I was wondering, without going into detail, just kind of categories, what the reasons for removal of...there was quite a few removals that are here, and I was wondering if you could give us some broad categories of reasons why you are voluntarily removing these.

DR. CUMMINGS: Well, generally, there is still limited use in some of these areas, but generally, there are adequate alternatives, and in some cases, there...they may be a identified as a critical, very niche use of the product, very small volumes, but

in some cases, they may be aligning with some of our...the vulnerable areas that our experts have...have identified, for instance, in Florida. There are some uses that just fit the Florida use pattern that we're proposing to remove. Okay?

So, I think broad categories, it's limited use, adequate alternatives, and really, the predominant geography where that would be used is we're proposing to remove from the label. Those are kind of the two...two buckets.

DR. HEERINGA: Thank you very much, Dr. Cummings. And I think at this point, let's move on to the first of the scientific presentations, and I think Dr. Keith Solomon of the University of Guelph is here, along with Dwayne Moore, and Dr. Solomon will be up first.

Panel members, I...I think Dr. Solomon can confirm, but I'd let both individuals do their presentations before we open it up for questions.

DR. SOLOMON: Mr. Chairman, panel members, EPA staff, others, I am Keith Solomon from the University of Guelph, and I'm here at the request of FMC Corporation and a panel member of the avian panel that advised FMC on risk assessment, additional studies, and also modeling issues.

So, next to me, is Dwayne Moore who will present the modeling part of the presentation, but also at the table, Lou Best and Larry Brewer. Larry Brewer conducted many of the studies that were talked about yesterday and that we will touch on briefly today. Lou Best has extensive experience in field work and perhaps best answer questions from the panel members in that regard.

Dr. John Geisy has a longstanding teaching assignment in China, and he sends his apologies for not being able to attend.

The RED and the Notice of Intent to Cancel in 2006 and 2008 concluded that carbofuran poses an unreasonable risk to the environment based on effects on avian species. In coming to this conclusion, EPA used a TIM 1 model which predicted high mortality in some species of birds and was based on a number of conservative assumptions.

The TIM 1 model which was talked about yesterday is...is inappropriate, I think, for the use...for risk...doing risk assessments on carbamate pesticides, because, for one...just for one thing alone, the time step involved is not...not appropriate. But we did try to use the TIM 2 model, but, unfortunately, could not get it to function on our

computers. The TIM 2.1 model which we heard about on January 8th this year we have not been able to use.

So, based on that, we set up our own model which Dr. Moore will talk to you about a little bit later.

The avian effects advisory panel conducted a refined risk assessment, and we started off by identifying data gaps. We then commissioned studies to fill these gaps. We developed a higher tier risk assessment model, Liquid PARAM, and we also looked at other lines of evidence from real-world studies and incident data.

We have concluded that carbofuran can continue to be safely used on all of the crops considered in this...in the assessment. The exception to this...and you heard about this earlier...was for the unique situation where waterfowl gorge feed in alfalfa, and this is now being removed from the label.

All of the documents that support our discussions here today have been provided to the panel. The slides are in hard copy. There are some overview reports in hard copy, and there's also a CD which has all the information on...in PDF and other files. There's also a copy of the model, if anybody's interested in that.

So, our objectives were to define...to refine the risk assessment and to generate new data and also to incorporate this in a more definitive model to consider several lines of evidence, and this was based on, as you heard yesterday, advice that came from earlier saps in 2001 and 2004.

And for the studies that we developed, there are no guideline studies here. These are...these are really studies to understand the science and not yet used widely, so no guideline studies, and at least in my experience, if you take those protocols in to EPA, they will decline to comment on them.

So, we did studies on avoidance repellence, on the effect of dietary matrix, and rate of recovery of cholinesterase, as you heard about from Robert yesterday. We also incorporated in the model the significance of time distributed feeding and increased the number of use scenarios and also increased the number of species in the model, as Dr. Moore will tell you about later.

And these results were then verified...this is perhaps a touchy word, verified...against field data, but if you go back to 1992 guidance on ecological risk assessment, this is one of the points that they make about models, that they can be verified against

field data.

Just to explain some of the issues that we were looking here in terms of avian effects, when one thinks of a bird and hot it becomes exposed and how the carbofuran might get to the target site, there are a number of steps involved in this...in this process. Of course, the first of these is the uptake of the material by the animal and repellence, whether it's gustatory or symptomatic, can reduce uptake of the material.

And then, the other fact, it's quite different from a laboratory study where you dose an animal with a single gavage dose. Feeding would be spread over a period of time, short or long, depending on the nature of the birds involved, but all of these would change the way the material enters the organism.

Once in the gut, one can see that the absorption rate might be affected by the matrix that is present in the gut at the same time as the...as the substance, so if it's on food particles or in the water that's consumed while the animal is feeding, the matrix in the gut could reduce uptake into the body.

After that, metabolism...and this is well understood...can remove the material from the blood and the other organs, and then finally...and you can see

the diminishing size of the arrows...some material will get to the target site, cholinesterase in the central nervous system which, we know, recovers quickly via hydrolysis of the carbomanated enzyme via K3.

So, this results, really, in a...in a diminishing of the potential for adverse effects through all of these intermediate steps in the process.

These processes are additive and, possibly, multiplicative. We don't know. But all of them appear in...in the real world, and there's a sequence that you have to go through.

And the TIM 1 model really only addresses metabolism. It doesn't address these other factors that we've listed on this slide.

So, our first approach was to do a study on repellence and avoidance, and this is not captured in acute toxicity studies where a material would be administered in a water bolus or an air bolus. And, incidently, there's no formal guideline for this, but there is an OECD draft guideline from 2003, and there has been work done in the literature on this as well, and we used this as guidance to develop the protocol with a choice of uncontaminated and contaminated feed, as you heard yesterday.

Mallard was used as a test species,

consistent with the literature, and food consumption and spillage was very carefully measured. And if you need more detail on that, Larry Brewer will be able to help you out there.

To basically go to the results fairly quickly, what this shows here is...first of all, you heard yesterday that there was a...a change in the feeding pattern of the animals in both the controls and the treated animals, the animals in the...in the test. So...and this is probably because of the increased observation that occurred over the changeover time and the animals reacting to the presence of humans in the system, but it occurred in both the controls and the test organisms.

So, what we did here was to take the initial weight adjusted, because animals of different weight consume different amounts of food, and we took the zero day weights, and we did a mean reduction in food consumption relative to the controls. So, this is standard biological experimental technique, is to compare results to control.

And what you see here is a very significant reduction in food intake shown in these numbers below...zero would be the control...with increasing exposure in the diet. We then took this data and

modeled it on the...on the presumption that turned out to be correct, that there was a threshold of avoidance.

And this, on the y axis, you see the reduction in food intake rate which is abbreviated as FIR, and concentration in the diet in a log scale on the x axis, and there's a threshold of repellence or avoidance here at 3 mg/kg in the diet which translates to 0.119 mg/kg body weight.

And then...so, this would not be considered in the model below this threshold. However, exposures above the threshold we would use the...the slope of that regression there to factor this avoidance into a...a model which you'll hear about later.

We believe this was an appropriately conducted study. One of the suggestions was to scatter the food around on the surface to more directly mimic the environment, but it's extremely difficult to get accurate measurements if you do this or even if you put it in numerous feeders.

If you do it on an hourly time scale which would, we agree, would be very useful, the hourly disturbance of the birds in...in the cages would, I think, have a greater influence on the results than the actual chemical itself.

Starved birds, we don't believe it's

appropriate to use them. It distorts the initial feeding rate, and it's not realistic. Birds in the field would not starve themselves in anticipation of the carbofuran application.

There's no learning of the location of the food or contaminated food items, because the feeders were switched each day to prevent that from happening, and we heard yesterday some discussion about feeder location bias, and there was no consistent propensity to use left or right, and so, we had, I guess, right-wing and left-wing birds in our system, and we...I'll show you the data for that in a moment, but this was basically controlled for by switching feeders each day.

This is just a distribution of all of the birds used in the study color coded. I apologize for the Christmas tree-like effect here, but it's...so, the birds that are on the right-hand side of that line in the center, they were biased towards the right feeder consistently over the study. On the other side, they were biased towards the left feeder, and there's no obvious relationship here to the treatments that they were receiving or the control or the different doses in the...in the feed.

So, repellence and...and avoidance, this reduces the food intake rate at dietary concentrations

that are relevant to field exposures. It's not applicable to gorge feeding waterfowl, and...and we have never claimed that or...and we would not use it in that situation anyway.

The reduced food intake rate did not lead to mortality. The animals continued to eat, and they ate both the treated and the untreated feed but at...at a slower rate. The increased food...the increase that we might expect in food intake rate at...after cessation of exposure was only observed at the highest concentration, and, again, this is consistent with what you see in the literature.

I think also interesting is the fact there was no weight loss in the birds. They didn't gain weight, but they didn't lose weight, either, so they were able to maintain at least their baseline metabolic needs over the period.

The next issue I'd like to address, a lot of evidence here, is the absorption of carbofuran from out of the food matrix. The food...the food matrix is basically toxicologically inert, and any binding to this or just the mere physical presence of a matrix there will slow diffusion of any chemical into...through the gut to the body wall and then, of course, up...the subsequent uptake.

So, both of these factors may reduce the rate at which the chemical enters the body, and this, obviously, can have a significant effect when you have metabolism and recovery of cholinesterase operating at the same time.

The animals were given a bolus dose in a mixture, a slurry of water and food, by gavage. These were compared to animals that were given a water bolus which is common in toxicity testing. And this was the hypothesis we were testing, is there a difference between a feed bolus and a water bolus?

The control...you heard some discussion about controls yesterday. The appropriate control for this, in fact, is the food matrix bolus, because this is an unusual dosing technique. The water boluses are used routinely, and...and we know what they mean in terms of acute toxicity testing, but the food matrix bolus here was used as a control to make sure that the matrix itself and the handling the birds were receiving was not causing any adverse effects, and there were no adverse effects in the control.

Then we look at the data showing initially bobwhite quail and the increase in response to increasing doses of carbofuran via the water bolus route. When you give those same animals...or

not...sorry, not the same animals, but when you give bobwhite quail the slurry of the food matrix, you see it shifts the toxicity values to...to much higher concentrations or doses, in this particular case. You'll see no response in the matrix dosed animals there and only the initiation of response at this concentration here.

You see essentially the same effects in mallards, although there were fewer doses tested here because of availability of animals, but, basically, one sees the same general pattern.

But when you take a percent mortality...and this is in the bobwhite data...and you look at the dose of carbofuran in mg/kg body weight which would be then equivalent to the LD50 via a water bolus route, you'll notice the data there with an LD50 of 2.64. When it's mixed with a matrix, what you see is a different LD50.

Now, this doesn't mean that the...and I'm now teaching you to suck eggs here, I guess, but this does not mean that the...that there's toxicity. It means there's less exposure, and in conjunction with metabolism, there is less material reaching the target sites. So, 3.8 times less toxic.

This study, we believe, again was a good quality study. There was no initial regurgitation of

food. There were very careful procedures put in place to observe this, a white paper put under the animal cages so that anything that was regurgitated could be seen. There was some regurgitation of opaque fluids, not food matrix, and this was seen later and was probably a symptom related...in relation to the effects of cholinesterase inhibition on saliva production, et cetera.

There was a slight delay in symptoms in the matrix fed birds, but, of course, you needed a much higher dose in them anyway, but this was expressed within the 1-hour time step that was appropriate to use in Liquid PARAM, so this was used in the modeling.

So, the rate of absorption of carbofuran is significantly reduced from a food matrix, and, therefore, the use of acute toxicity test results such as the traditional water bolus or oil bolus, LD50, overstates the potential risks posed, and for this reason, we used a dietary adjustment factor that Dr. Moore will talk to you about in a minute in the Liquid PARAM model.

The last issue I wanted to just introduce quickly was the recovery of cholinesterase, and we heard a lot about that yesterday afternoon and more this morning. What this does is really gets around all

of these issues and focuses just on the target site which there's a well-known process that occurs here that you're already familiar with, but the key reaction here is the hydrolysis of the carbomanated cholinesterase which releases the serine hydroxyl to allow the enzyme to return to its normal function, and this is governed by K3.

This is dependent on the tertiary structure of the enzyme itself, and the group, the carbamyl group here, which is the same for most carbamates and is consistent across many of the carbamates.

So, what you're really doing here is looking at a combination, in a sense, of metabolism, because the chemical is now in the animal, and the target site, and this is important, because this is the target site. This is the mechanism by which the chemical is directly toxic. So, this integrates a very important effect measure that is relevant to the assessment in point of mortality.

So, in this study, we used animals that were dosed with water, so there's no matrix effect, and the brain cholinesterase, acetylcholinesterase, is measured at time intervals after dosing, and then recovery assessed against control values. So, plotting the cholinesterase activity on the y axis in terms of brain

weights and time since initiation of exposure, when you look at the controls, what you see is a mean of around 12, with a 95 percent confidence interval going below and above that, so that would be the range we would normally expect to see the controls in.

At the lowest dose tested, we saw rapid recovery into the control range. At...and this, with increasing dose, became longer.

Now, the reason for the increased length here is not because the cholinesterase is somehow changing. It's because there's a combination here of metabolism trying to catch up, and if there's a larger amount in the body, if the enzyme is reactivated, then there still may be enough carbofuran to re-inhibit again which would lengthen the recovery time.

These recovery times were used to calculate the half-lives, but it's perhaps interesting that the half-life of recovery of cholinesterase is used as sort of a forensic threshold, and in the...in the trade, if an animal is above half of the control value in terms of brain cholinesterase, it will be likely to survive. So, this would be an indication of no permanent adverse effect.

So, using this relationship between the half-life on the y axis and the dose on the x axis in mg/kg

body weight, we chose from this relationship a conservative value of 4.4 hours as the half-life for integration for recovery into the Liquid PARAM model.

So, it's a rapid half-life. It's...it's a little bit conservative, and it's definitely quite different from EPA's elimination half-life which is based on metabolism in chickens that was used in TIM 1, and that is...it's probably inappropriate to use that type of data for carbamates because of the very rapid recovery of cholinesterase in those organisms.

So, with this, I would pass over directly to Dr. Moore, and with the permission of the panel, we'll hold our questions until the end of his presentation.

DR. HEERINGA: Thank you, Dr. Solomon. Dr. Moore?

DR. MOORE: I thank you to the panel, to the chairman, and interested observers for the opportunity to speak this morning. My name is Dwayne Moore. I'm with Intrinsik Environmental Sciences in Canada. As...as with Keith and the rest of the panel, I was asked by FMC to assist with the avian risk assessment for carbofuran.

What I want to talk about over the next 45 minutes to an hour, very briefly, a little bit about model development history, talk about the exposure

assessment, and that would be the majority of my talk. Will talk about model structure, the inputs, and also spend some time talking about how we evaluated model performance. Then finish with discussion about the risk characterization and results that we obtained, the results that we obtained when we looked at better lines of evidence, and then have some conclusions and thoughts for the panel to consider.

Just for your information, the...the model itself that I'm going to spend most of the time talking about is described in, I would consider, in exquisite detail in the...the refined risk assessment report that was included in your package. It's Moore, et.al., 2007 is how I refer to that. If you're like me, you have a social life...or don't have social life, you would consider it exquisite, and otherwise, you would consider it excruciating.

The exposure assessment is described in chapter 3, the effects portion of the model is described in chapter 4, and the risk portion of the model is described in chapter 5.

A little bit of background, and you've heard some of this yesterday and this morning. TIM Version 1 was originally developed by EPA and submitted to the science advisory panel for review in 2001, and as you

heard yesterday, EPA believes that that review plus the subsequent review in 2004 of a different version of the model allows them to then us that model and not have to worry about questions concerning model structure for this carbofuran assessment that you're charged with reviewing here today.

But I would like to suggest, at least, that the mere act of reviewing models does not constitute endorsement of the models. Lou Best and I were both participants in those science advisory panel meetings, and there was no endorsement of those models.

What there was was encouragement to continue the model development. I think that's a very important point. Avian risk assessment models for flowable pesticides are just really getting going. That model that was developed in 2001 was the first probabilistic avian risk assessment model for pesticides, and so, as you would expect with any young science, there is as need for continued development, maybe a need for continued development going forward from today and...and I hope five or six years from now, we're talking about new versions and...and better models than what we have before us.

At that science...science advisory panel meeting in 2001, as I said, the panel was encouraging,

but they made many suggestions for improvement of that model. And as you heard from Keith, new studies have also been commissioned and completed by the registrant, and there's new information available in the literature that are relevant to model development.

So, it...it's...it seemed an opportunity, then, for FMC to take advantage of the model development that had already occurred, the recommendations that had been provided by the science advisory panel, and with the new information that had been commissioned by the registrant as well as what's in the literature, it seemed time to develop a much more refined risk assessment model.

That's what FMC commissioned this panel to do. That model and the accompanying avian risk assessment was presented to the Agency on July 12th, 2007. Subsequently, we submitted the full risk assessment report to the Agency on September 7th, 2007, and the model and the accompanying user guide were submitted to the Agency on October 19th, 2007, and I believe you have all those documents as part of your package.

EPA recently used TIM Version 2.1 to investigate the relevance of some of the studies that FMC had submitted to the risk assessment conclusions,

but I would caution that TIM Version 2.1 was not used in the ecological risk assessment that you're charged with reviewing here, the 2005 report, and I think even more importantly, that model has not been released, nor has information on model structure and inputs been provided to the public, the SAP, or the registrant. And so, we are in no position to evaluate the model structure or the inputs or...or its outputs.

And a final caution, in...in the comments we heard yesterday, there was the argument put forth that the fact that the outputs from TIM Version 2.1 and Version 1 tend to agree with each other somehow constitutes validation of the model. I'd have been surprised if they didn't agree, for the most part, because they're obviously heavily related models. The fact that they had similar outputs means that they either did things really well and they both do it really well, or they do things badly and they both do it really badly. It has no relationship to validation against field data.

Since completing Liquid PARAM, we have indicated our willingness to assist EPA with the use of the model or answer any questions that they may have. As you can see from up above, that was several months ago.

I was a little disappointed to hear yesterday that, you know, when they first evaluated the model, they had some difficulties running the model. We were never contacted to help them through that.

This model was developed in Excel with Crystal Ball added. Anybody who uses Excel extensively would know that you sometimes need to have exact matching versions of the model. Microsoft does not make them backwards compatible in all cases. So, sometimes you have to make sure that li...library references are checked off and things like that. All very easy to do, and with a phone call, we would have been hap...happy to assist EPA with that.

As EPA noted yesterday, there are no errors in the model code once...once they had a chance to work with the model.

Liquid PARAM or what it stands for is Liquid Pesticide Avian Risk Assessment Model. That's what was developed for this assessment. And we did incorporate many parts of TIM Version 1 in this model.

There...as I said, the panel was very encouraging in 2001, and so, for those things that they...they were particularly supportive of, we kept those pieces. But then we moved on and actually systematically went through all the recommendations

provided by the science advisory panels and tried to incorporate those that we could.

The model was expanded to include a number of additional components related to things like avoidance, the toxicity adjustment factor for the dietary matrix, and so on. We added a number of crops so that we'd be able to evaluate all the critical uses that John talked about for the amended label as well as alfalfa, and we added a number of focal species. We wanted to make sure that we had bird species in the model that frequent those six different crops that we are most interested in.

The model has gone...undergone extensive sensitivity analysis, and I'll talk about an evaluation of model performance that was conducted.

Some of the similarities to TIM Version 1, we kept three original crops, corn, cotton, and alfalfa. Similar with the original focal species that were in TIM Version 1, and we have three application methods, in furrow, banded, and foliar broadcast.

Much of the information about the bird species themselves, at least the focal species that are common to both models, we kept, such as dietary composition and body weight, and gross energy of different prey items and the efficiency with which they

are assimilated by birds. That information was retained.

The drinking water scenarios in the two models are the exact same. So, we have puddle scenarios day of and day after. We also have a dew scenario for both. The drinking water ingestion rates, concentrations in dew and puddles and so on, the same.

The food intake rate equations and dietary nomograms aren't quite the same, but they're pretty similar, certainly a similar approach, but we updated the food intake rate equations to account for more recent data, and we also include the error term associated with those allometric equations in our modeling which TIM Version 1 does not.

Degradation rates in water and food are the same. The effects component, that notion of using species sensitivity distribution to generate hypothetical risk curves for a sensitive, a median, and a tolerant bird species, that component is very similar to what...to what is in TIM Version 1.

And, finally, the output from our model is the same as TIM Version 1. Essentially, what Liquid PARAM does is it determines the fate for each of 20 birds on each of 1000 fields for whatever use pattern you're investigating.

It is a field level model. Dr. Sample commented or asked yesterday whether the model, TIM Version 1, can say something about landscape risk, whether it's a mixture of fields that might be treated. This model does not do that, nor do any of the TIM version models.

The next few slides, I'm going to go through some of the major comments that the science advisory panel provided on TIM Version 1 and indicate how we responded, very briefly, in developing Liquid PARAM. Subsequent to this series of slides, I will then go into detail about the major components in Liquid PARAM.

So, one of the first comments that science advisor...the science advisory panel had in 2001 was that the use of two time steps per day, that is, 12-hour time steps, in TIM Version 1 is overly simplistic, and that's because of the rapid processes associated with compounds such as carbofuran. So, Liquid PARAM has a 1-hour time step, as does TIM Version 2.0 and 2.1.

The panel commented that the use of an on/off approach for each 12-hour time step misrepresents how birds forage in the field. What happens in TIM Version 1 is that a...a draw is taken from a distribution by random chance. That is entered into a binomial

distribution and, by random chance, the bird is assigned to...for each time step as to whether it forages entirely on the field for that time step or entirely off the field for that time step.

In reality, birds forage...make many foraging trips in a time step, even a 1-hour time step, and they...they can quite commonly move to areas on the field or off the field, depending on where they're nesting and...and...and their preferences.

So, they're...they're not necessarily going to spend one 12-hour time step completely off the field and then, during a subsequent time step, completely on the field. I think that's an unrealistic assumption.

So, this is just shown graphically here. This is a horned lark nesting on the perimeter of a field, and in any given time step, whether it's 1 hour or a longer time step, it can make multiple foraging trips, and it can go sometimes into the field or sometimes off the field. This is a fairly simple concept.

The panel noted that the distribution of individual foraging behavior on fields is different from the distribution average population behavior between fields. I think that's fairly obvious.

The data, the census data that you heard

about yesterday where you do in and do counts of birds on and off the field, essentially is a representation of average population behavior for that field. To then somehow assume that that represents the distribution of individual foraging behaviors within a field is not supported.

We partitioned these two sources of variation in Liquid PARAM, and I'll describe how that was done in a...in a few slides.

A similar concern was raised by the SAP with regard to dietary residue levels. As you would expect, there's variation between dietary resi...in dietary residues between fields and within fields. In TIM Version 1, those two sources of variation are merged together. In Liquid PARAM, we partition those sources of variation, and, again, I'll talk about that.

The SAP noted that it would be more logical to look at recovery at the active site of toxicity which Keith talked about, recovery of acetylcholinesterase inhibition, rather than whole body elimination, and FMC commissioned a study to quantify that, and those results were incorporated in Liquid PARAM.

The SAP noted that in birds, the regurgitation could be important in reducing risk. A

study was conducted to determine that and quantify that behavior, and those results were incorporated in Liquid PARAM.

The SAP noted that acute oral sites do not account for the effect of a dietary matrix for an absorption rate of the...of a compound into birds. As Keith described, a study was conducted to better understand the importance of dietary matrix on toxicity to birds and the results incorporated in Liquid PARAM.

And, finally, the panel noted that field validation of a model, particular a model that's early in the development for the...for this science of avian risk assessment, is critical. As Dr. Bradbury alluded yesterday, validation is kind of a hoary concept. I like to think of it as evaluation of model performance. I don't think you can ever fully validate a model, but we do want to have some idea about performance relative to what is observed in the field.

So, a little bit about Liquid PARAM. This is the 30,000 foot view of Liquid PARAM. We certainly don't have enough detail or time to get into the details of the equations and so on, although there are over 10,000 equations in the model, so it...it is a beast. Takes about two and a half hours to run.

The first component of...of the model...and

I'm going to talk about the exposure side of the model here...is to define the pesticide use scenario. Here you would specify the crop, the application method, the application rate and so on, and that information determines what the initial concentrations of carbofuran will be in food and water on the field.

Now, this model has a time step, and it continues for 28 days. So, it's an hourly time step. It goes for 28 days. The reason why it is twice as long as TIM Version 1 is this model can handle two applications, so we had to extend the...the time frame out.

So, we want to then know something about how those initial concentrations in food and water change over time. To do that, we need some information on degradation rates, and when you combine those degradation rates in food and water that have been measured with the initial concentrations in field, what you get is a picture of concentrations in food and water over time.

On the...the biological side of the model, there are a number of focal species associated with each crop use that you can choose from. Once you select a species, you can then select a foraging behavior, whether you want to look at gorge feeding or

more even feeding throughout the day. And so, that information then determines the ingestion rates over time for each hour of each day in the model.

Knowing what's in the dietary items and in water over time and knowing ingestion rates over time allows us to then estimate hourly pesticide dose. So, we have an hourly pesticide dose for each of the 24-hour time steps per day and 28 days in the model which is 680 time steps.

As Ed and Christopher described yesterday, the birds, however, carry over some of the preceding doses in their body, and that's a function of rate of metabolism. So, knowing something about the rate of metabolism and how much dose they've already received, we can specify a body burden. Then, in the current time step, a new hourly pesticide dose comes in, and so, we have something called hourly retained dose. That's the current dose plus what was retained from before. Hourly retained dose is the same as a body burden.

So, that's the exposure side of the model. What's carried over from the exposure side of the model, that hourly retained dose or body burden for each time step in the model, and what the model then does is it searches through all of the hourly time

steps and finds the maximum retained dose, the maximum body burden that occurred at whatever time period it occurred at following application, and that is the exposure metric that will be used in determining whether the bird lives or dies.

And now, the effects side. As was described yesterday, for almost all of the focal species, we do not have toxicity data. We did have it for northern bobwhites, and, as mentioned, there's also data for red-winged blackbirds, and so, if that information was available, we could use that dose response curve, and that...that would be used in the estimation of risk.

For the remaining focal species, though, we did not have species-specific toxicity data, so we used that sensitivity distribution process described yesterday, and I'll show a picture of that later on. And knowing the LD50 for the 5th percentile species, a very sensitive species, for the 50th percentile species, and for the 95th percentile species and a slope where we took the average slope measured across all focal species or across all tested species, just as EPA did, we can come up with three hypothetical dose response curves that represent sensitive, median, and tolerant bird species.

And for each simulation that we did, because

we didn't know the sensitivity of...of those focal species, we did all three, and that at least allows you to get an idea of what the range of risk could be for untested species. This is all very similar to what EPA did.

So, we have a maximum retained dose, we have a value randomly drawn from each dose response curve, and it's very simple. If exposure is greater than effects, the bird dies. If exposure is less than effects, the bird lives.

And then, this simulation is repeated for 20 birds on each field, and then the whole thing is repeated for 1000 fields. And on the risk results we show are just results for those 20,000 birds combined.

Talk a bit...a little bit about time step. In the arguments yesterday and in the comments previously submitted to the panel, EPA stated that decreasing the time step from 12 hours to 1 hour did not impact the exposure estimates, and that's a rather surprising result, given how fast some of the processes are associated with exposure to carbofuran, when you consider the recovery rate from acetylcholinesterase inhibition, decay in the field, avoidance behavior, and so on.

So, let's consider a really simple example.

This is hypothetical. A food intake rate of 1 kg, wet weight per kg body weight per day. We'll just assume for simplicity that the bird feeds on only one item, and that item had an initial concentration in the field of 5 mg/kg wet weight. We'll further assume a half-life on that dietary item of 3.1 days. That is the measured half-life for carbofuran on seeds and insects in the field. And we'll assume a metabolism half-life based on the brain acetylcholinesterase recovery of 4.4 hours, and that was based on the...on the study that Keith described. So, these are all values used in our assessment.

Here are the results if we have a 12-hour time step and a 1-hour time step. On the x axis is time since application, going from zero hours up to 250 hours. On the y axis is body burden or maximum...or dose retained in mg/kg body weight. The blue curve is the results for the 12-hour time step; the red curve is the results for the 1-hour time step. Note no other differences between these two applications.

What you find is that the peak is much higher with the 12-hour time step, peak body burden, and then, of course, it started to decline. In fact, the maximum body burden with the 12-hour time step is 5.23 mg/kg which is more than double the maximum body burden with

a 1-hour time step of 2.4 mg/kg. And it is that maximum body burden that is the exposure metric used to determine whether a bird lives or dies.

And we have not considered avoidance in this analysis and some of the other rapid processes that go on when you estimate exposure and risk of carbofuran to birds. So, this very simple example illustrates the importance of time step.

Daily foraging behavior. As I mentioned, birds vary somewhat in their foraging behavior over time during the course of a day. To try to get a better understanding of that, we reviewed the literature to determine how daily foraging patterns vary from species to species.

You can see there's a long list of passerine bird species for which that information has been determined, been determined over a number of years and generally involve nesting birds. And what we found was that most passerine bird species, during nesting, have relatively even feeding throughout the day with slight peaks early and late in the day.

This isn't really surprising. When they're nesting, the...the nestlings have high demands, and the...and the adults are quite active in trying to...to, quote, provide for the nestlings as well as

for themselves, and so, they're...they're required to feed throughout the day to...to be successful.

Both peaks in the early and late in the day are just small peaks. It's relatively even feeding throughout the day but a slight bubble in the pattern.

Waterfowl may exhibit gorge feeding...this is a little bit different feeding behavior...particularly during migration. Because they are flying for long hours, when they...when they do alight on fields, they may exhibit gorge feeding, and this has been demonstrated in a number of studies.

So, in our model, we have two options to explore these different range of foraging behaviors. On the x axis is time. There's an overnight time step right at the far left, and then we begin at 6:00 a.m. in the morning and continue to sunset at the end of the day.

For those passerine bird species that are nesting, we would expect something like that bimodal feeding pattern shown with the purple diagonal, shown there. A slight peak in the morning, a slight peak in the evening, and a little bit lower intake the rest of the day.

For waterfowl, what we assumed in the model is...was essentially a gorge feeding pattern, a large

intake in the early morning and a large intake later in the day. The y axis is proportion of total daily intake.

So, in Liquid PARAM, for our waterfowl analyses, we assume that gorge feeding pattern shown in black. For the remaining bird species, we assumed that slight bimodal distribution shown in purple.

It's interesting to contrast that with what is in TIM Version 2.0. Because TIM Version 1 has as 12-hour time step, there is no consideration of variation in daily foraging pattern, but in TIM Version 2.0 and 2.1, there's a 1-hour time step, so it is possible to consider variation in daily foraging behavior.

And this...this figure here is based on a report prepared by EPA and submitted to the science advisory panel in 2004 for their consideration, and what this shows is the kinds of patterns that their model generated for individual birds throughout the day.

And you'll note that those patterns...and these are generated through a fairly sophisticated randomization model...is that there's actually no feeding in the middle of the day for the example shown here and fairly large peaks in the early morning and

later in the day. And this is much more or at least approaches gorge feeding pattern, and...and they used these patterns for non-waterfowl species.

So, it's interesting to note that even though we're considering similar bird species, very different assumptions about daily foraging behavior.

Although the...the statistical model used to generate these distributions is pretty sophisticated, it's not in any way based or corroborated by field data. There are no citations in their report referring back to field observations to support these distributions.

So that...and that gorge feeding pattern, as you'll find out later, or...or approaching a gorge feeding pattern almost certainly results in higher risk estimates, as I'll show later.

So, that's daily foraging pattern. I want to talk about proportion of time that birds spend foraging in fields and foraging out of fields. This is a major consideration in estimating risk to birds.

If you go back to the original data set, the proportion time data for bird species is based on the proportions of birds observed in and out of fields. Lou Best was involved in reviewing much of that literature. He's sitting here. And so, if they...this

is obviously a very simplistic example, but if the field observer noted 3 birds within a field and 3 birds outside of a field, then the proportion time foraging in the field for that population, the average PT value, would be 0.5. That's a very simple example.

So, each datum is, thus, an average PT for the population of birds on the field.

PT varies, though, quite a bit between fields even with the same bird species, and it also varies between row crops versus a field crop such as alfalfa, because alfalfa is quite a different crop. Birds actually will consume alfalfa.

So, here's another example where we have 6 birds inside the field, 2 birds outside the field, so the average PT for that population would be 0.75.

These differences arise because the relative attractiveness of the fields themselves and the surrounding habitat varies from field to field. So, in some areas, the edge habitat would be far more attractive to the species of interest, and so they won't spend very much time in the field. In other areas, the field itself might be more attractive to the birds.

TIM Version 1 does not distinguish between population or between field variation in proportion

time foraging in fields versus the variation that you would expect to find between individuals within a field.

For each individual in each field, what we did is a distribution was developed that captures that between field variation and average PT. We sample from that. That determines...I'm sorry...for TIM Version 1, that determines the probability for an individual within a field of being on or off the field for that time step. So, essentially, variation between fields, the average PT is being used to determine for each time step whether an individual is on or off the field.

Those sources of variability were partitioned in Liquid PARAM. I'll show how that was done momentarily, and...and reason we did that is it re...represents a more appropriate use of the data. It respects the source of data and...and captures the variability as its represented in the data.

I would still caution, as you heard yesterday, this variable still is uncertain. The mere fact that a bird is in the field for a proportion, a certain proportion of the day, does not necessarily equate to that same proportion of their diet being from that field. That's an assumption. It's an assumption for all the TIM version models as well as our own.

So, how did we do it in Liquid PARAM? On the upper left, we have a typical result for...from the census data that...that Lou Best and co-authors collected information on. So, this is for dickcissel, and this is for row crops.

And the little red dots shown here on the x axis are the actual observations for individual fields or groups of fields in the same...similar location. What you see for dickcissel is that you have some fields where the birds rarely spend time in the field...that would be down at the zero end...and you have other fields where all of the individuals were almost always on the field. Quite a range of behaviors even though this is the same species foraging in row crop fields.

What we did in Liquid PARAM is we fit or estimated a distribution that would represent that variability in average population behaviors between fields. You'll note that this distribution is weighted more towards the conservative end, that is, assuming that birds spend more time foraging in fields. So, in all cases where we had rather limited data such as in this example, we were conservative.

Let's take an...a hypothetical example here and say field number 4. What we do is we randomly

chose a value from that distribution. We combined that randomly chosen value and assumed that a minimum of zero and a maximum of 1 would represent the variability of individuals within field number 4. We don't have that information, so we maximized uncertainty by assuming the two extreme values.

So, that was used to characterize a distribution for field number 4, and that's shown here in bright...in the thick orange line. So, if you choose that value for field...field number 4, assume a min of zero and a max of 1, what you get is this distribution here shown as the thick orange line. What that indicates is that for individuals in field number 4, the majority will spend more than 50 percent of their time foraging in the field. A few will forage a lot in the field, and a few won't spend much time in the field at all.

And you repeat this exercise for all of the fields. You'll get different curves that represent proportion of time foraging in the fields within a field. And in some fields, by random chance, almost the entire population will always be in the field. By random chance, other fields will spend...will have all the individuals barely spending any time in the field.

Continuing on with this example, so for our

field number 4, we would next draw 20 values from that thick orange distribution and come up with individual PT values for each bird in field number 4. That's shown here. So, we have a bird that spends about 27 percent of its time foraging in the field. We have the majority of birds somewhere around 60 to 75 percent of their time in the field, and a couple of birds that spend almost all their time foraging in the field.

So, what we've done is we have effectively partitioned between field and within field partitioning dat...or foraging behavior in the fields.

This process was repeated for all the other fields. It's quite a laborious process. You can see in chapter 3 the exposure assessment part of our refined assessment, all the distributions that we came up with, all these green distributions that we came up for each of our focal species for row crops and for field crops such as alfalfa.

Dietary residues. As indicated yesterday, TIM Version 1 samples from those between field residue distributions at every time step within every field. So, much like the case with proportion time foraging in the field, the original data represent variability between fields in dietary residues.

So, that information is then being used in

TIM Version 1 to look as an example of the variability that you would get within a field and between time steps. And because of this, you often get several fold increases in dietary concentrations from one 12-hour time step to the next which seems a little bit counterintuitive, given the rapid decay of the compound in the field.

And it's just by random chance. You would have a distribution. By random chance, you could select a rather low value in the first time step and then, in a subsequent time step, by random chance, select a higher value.

It's important to remember that those original nomogram distributions by Fletcher, et.al. and Garner, et.al. were based on between field variability, and you would expect between field variability to be important, because there are differences in slope, soil type, operator skill, quality of the machinery, and so on. And you would expect those differences to be much more important between fields than you would within.

Just as a side comment, it was noted yesterday that our insect residue values for the nomogram differed from what EPA used in TIM Version 1. We used the result from Fisher and Bowers, just as EPA did, but we removed the granular value result, because

it obviously is not apply...applicable to a flowable pesticide like...like we're looking at. And there were a number of studies where they didn't specify the application method, and being...wanting to be able to be specific to in furrow, banded, or foliar, we removed those studies from our distribution that we developed.

Those calculations are all spelled out in gory detail in chapter 3 of our document.

So, Liquid PARAM samples from each nomogram to determine initial residue concentrations from each field and then declines them thereafter due to degradation. We basically assume that intrafield variability is unimportant.

As you found out in that...in the documents that you received prior to this meeting, the EPA believes that intrafield variability is important, and they show that there are a number of studies that have been conducted to determine coefficients of variations within fields. They range from 0.08 to 0.93 for vegetation, so the ratio of standard deviation to the mean varied from .08 to 0.93 for vegetation, 0.23 to 0.71 for insects. These val...these coefficients of variation are much lower than what you would find for between fields, as you would expect.

But I think it's important to remember that

birds don't just go into a field once during a 12-hour or 1-hour time step. They go in multiple times. They make multiple foraging trips, and as a result, they spatially and temporally average their exposures even within a relatively short 1-hour time step.

Based on a review of the literature...and all of the citations are provided in our document...we found that birds typically make three to about 4 leaf foraging trips per hour. So, let's just consider a worst case example.

The highest coefficient in variation that was found by EPA, that 0.93 value, and we'll assume a minimum number of trips per hour, 3 trips per hour. That would...if you add more trips per hour for a lower coefficient of variation, you would expect even more spatial and temporal averaging.

If you just characterize the distribution for residue concentration as shown on the X axis, that blue dash line would represent the...the dispersion that you would expect within a field with a coefficient of variation of 0.93. Now, if you assume that the bird makes 3 foraging trips per hour and thus comes up with a spatial average, and you do this for a simulation, say, 10,000 times, what you find is the distribution tightens up quite dramatically.

I'm sure the statisticians find this to be a really simplistic example. But what you find is a...a much stronger indication of centrality in the distribution, much smaller dispersion in the distribution, and as a result, intrafield variability is a relative minor issue once you actually account for how birds forage within a field. And remember, this is a worst case example.

So, I'll just give you a pictorial representation of...of how Liquid PARAM works then. We take those between field nomograms, randomly sample from them for each field. We do this for each of the dietary items, such as grass, foliage, insects, seeds, and so on.

Here are some randomly chosen values for grams in mg/kg for the first 8 fields. You can see they vary by quite a bit. There is a lot of between field variability. Similar for forage on...in this column.

And then what happens in Liquid PARAM, this is for field 1, and we have an initial concentration, as specified in the...on the upper left there, and then it is just decayed through time according to the degradation rate that has been observed for grass in laboratory studies. So, there's no within field

variability once the application occurs.

The reason you see zeros up here is in Liquid PARAM, we can specify what time of day the application occurs. In this particular example, the application occurred at noon.

Avoidance behavior. You heard a lot of discussion about this yesterday. Keith described the study itself. In Liquid PARAM, we incorporate a 1-hour time lag, so it's the preceding body burden that determines how much avoidance behavior they'll have in the current time step. That's a 1-hour time lag.

In these studies that were conducted on behalf of the registrant, we found that...that recovery begins, actually, in about 30 minutes, so this is a fairly conservative assumption. Dr. Sample raised the issue yesterday or asked a question about whether the error term in this regression model is incorporated in Liquid PARAM, and it is not. It would be a computationally challenging exercise to do that, but I think it might be something worth exploring in the future.

So, what is that regression relationship? What we have on the x axis is average dose. This is from the experiment. And on the y axis, reduction in food intake rate. There's no effect at all on food

intake rate at zero, and what you find is at very low doses, there was actually...indicates no change in food intake rate.

Then at a certain dose, 0.119, there's a threshold. Thereafter, as dose increases, there's an increasing amount of reduction in food intake rate.

And so, in the model happens...is at the preceding time dose, we have a body burden. To convert it...so, what would normally happen is you would then find that dose, read up to the curve, go across to the left, and figure out what the reduction in food intake rate will be for the current time step.

Now, as...as indicated yesterday, the...the laboratory study was not able to determine food consumption on an hourly basis. That would have been too invasive. It was done on a daily basis, but the time step in the model is an hourly time step. So, we had to make an extrapolation.

The way we did that is if you go back to the original protocol for the laboratory study, the exposure period is 8 hours per day. It was 8 hours light, 16 hours dark, and mallards wouldn't feed in the dark.

So, what we did is then with the preceding dose for the preceding time step, the 1 hour, we would

multiply it by 8, then go to this model, read off the ax...x axis, so say 0.6 mg/kg body weight per day. Go up to the curve. That would be roughly a 35 percent reduction in food intake. Apply that to the dose for the current time step, and continue on. Okay?

So, that's how we converted from...between the two types, between the laboratory study and the model. That's exactly how Ed explained it yesterday later in the day, so the EPA did have a correct understanding of it.

That is an extrapolation uncertainty. Obviously, we are assuming basically even feeding throughout the day, for example. We don't really know that.

Species sensitivity distribution. You had some questions yesterday about slopes and how much difference there...there is between sensitivities when you assume the 5th, 50th, and 95th percentile of sensitivity, so I thought I'd throw this figure up. Basically, what we have on the x axis is dose shown here in mg/kg body weight. Percent mortality here. And if you fit a distribution to the LD50s that have been determined for other test species, you can get a 5th percentile LD50, 50th percentile LD50, and a 95th percentile LD50.

And then, if you go ahead and obtain all the slopes from those toxicity studies...and we averaged them just as EPA did...you get an average slope as shown here, and that information, the LD50 and the slope, can be used to generate this dose response curve for a very sensitive species, for a medium tolerant species, and for a highly tolerant species. So, that's how the SSD approach works.

And the major difference between what we did in our effects component and what is done in TIM Version 1 and TIM Version 2.0 and 2.1 is these three curves are shifted to the right along this x axis by a factor of 3.8, and that's to account for the differences in toxicity between and oral or a water bolus dose test that's done with the standard acute oral test and what you find with the dietary matrix as the vehicle for exposure.

Sensitivity analysis. As described in section 3.4 of our refined risk assessment, we conducted extensive sensitivity analyses for Liquid PARAM. We created two exposure scenarios. One was a high exposure scenario involving the maximum application rate for potatoes in the Northwest and a lower exposure scenario which involved application at a much lower rate in cotton.

And then, we looked at two different bird species, one that would be expected to spend a lot of time in the field...horned larks spend a lot of their time foraging within fields...and we applied that to the high exposure scenario. For the low exposure scenario, we...we focused on a bird species that wouldn't be expected to spend much time in fields, and that was the American bobwhite. So, we...we kind of have two extreme scenarios that we used in our sensitivity analysis.

When you do those analyses, we varied quite a number of different parameters to find out which ones were the most important. What you find is that there are four key variables that have a dramatic impact of predicted mortality of bird species. They are foraging pattern...that's the difference between gorge feeding and that much more even feeding pattern throughout the day. That is critically important. As gorge...if you strictly keep everything else constant and compare the results between even feeding throughout the day and gorge feeding, gorge feeding will have much higher mortality.

Rate of metabolism, as you would expect, is important. Whether you use a half-life of 4.4 hours or 9.4 hours, as used by EPA, makes a difference.

Incorporation of avoidance behavior makes a big difference, and incorporation of a dietary matrix adjustment factor makes a big difference, and I'm showing that particular example here to the right.

And we have the results for the high exposure scenario for horned lark on potatoes. What we have on the x axis are the results for assuming high sensitivity of the species, median sensitivity, and low sensitivity.

For assuming high sensitivity, what you find is that if you don't incorporate the adjustment for the dietary matrix, mortality is quite high. You incorporate that dietary matrix adjustment factor of 3.8, the mortality is...predicted mortality is reduced by over a full third. So, this is a very important variable.

For the more tolerant bird species, it's not as important. We don't predict much mortality for horned larks in potatoes if they are of median sensitivity or if they're a highly tolerant species whether or not you use that matrix adjustment factor.

We weren't able to do sensitivity analyses in Liquid PARAM to investigate the importance of time step. That would be a great structural reconfiguring of the model, but based on that simplistic analysis I

showed you earlier, I would expect that time step...time step is critical in explaining differences in predicted mortality between TIM Version 1 and Liquid PARAM. And I would also expect that the different assumptions that TIM Version 2 and Liquid PARAM make regarding daily foraging behavior is critically important, because I know we have a much more even foraging pattern for non-waterfowl species than does TIM Version 2 or, presumably, 2.1.

And there are also differences between EPA models and our model with regard to how proportion time foraging in the field is dealt with, dietary residues is dealt with. Food intake rates have been updated somewhat in our model, and we also consider the error term. So, there are a number of other differences between the models that can also explain the dramatic differences that you're seeing predicted mortality between the two models.

Okay, evaluation of model performance. You heard...you heard about some of the field studies yesterday. We reviewed the literature for field studies involving application of carbofuran and then monitoring the impacts on avian species. In reviewing the literature, it became apparent that the most useful studies for actually quantifying mortality in the field

was Jorgensen, et.al., 1989 and Booth, et.al., 1989. These were studies you heard about yesterday.

Those studies were conducted in Nebraska and Texas-New Mexico for corn, in Kansas-Oklahoma for alfalfa. These studies determined pre and post-application bird mortality in treated and in control fields. The experimental design was 8 times 2 paired plots.

There was no randomization as to which of those paired plots was control or treatment. Essentially, what happened was a number of farmers were identified that would apply carbofuran to their fields, and then what the study authors did is they looked around for a very similar field in terms of surrounding habitat, surrounding...and the type of bird species that used those fields. So, it was a paired control/treatment.

And this was 8 times 2 paired plots per state. Those paired plots were separated by at least a quarter of a mile, so, hopefully, that minimized birds foraging in both the control and treatment fields.

The protocol used for these studies followed EPA guidance and took account of EPA comments that had been provided on...on preceding field studies to the extent that they could.

So, for example, dogs were used to assist in carcass searches, and that...and dogs, they don't...they don't care if it's a small little bird or a large bird. They...they move by smell, so there's no size dependence in...in their ability to find birds.

And it's really important to note here that the results for every single plot were corrected for carcass search efficiency and the disappearance rate of birds from those fields. It was determined in every single plot in these studies.

And so, when we determine percent mortality for each plot, we corrected for these search efficiencies and disappearance rates. So, all those arguments you heard about well, might not be able to find every single dead bird, we corrected for that.

It was a really well conducted study. There was a lot of information collected, and that's what allowed us to do a lot of these appropriate manipulations of the data.

You heard yesterday that the control plots may...may not be true control plots in the sense that they had no pesticide applied. That is true. Synthetic pyrethroids were used in the corn control plots, and chlorpyriphos was used in the alfalfa control plots.

I wouldn't expect any issues with the synthetic pyrethroids, because they have low toxicity to birds. The chlorpyriphos is toxic to birds, and so, that's an issue.

Note that those pesticides that were applied in the control plots were applied two to three weeks before carbofuran treatment.

Also important to note that edge fields were treated with a variety of pesticides. Some neighboring fields were treated with a var...a variety of pesticides but not carbofuran. Again, something to consider.

But in the end, as I'll show in...in the next two slides from now, there was little avian mortality on control plots. And we will show you the results corrected for mortality on the control plots and not correct for mortality on the control plots, and you can judge for yourself which is the appropriate method, but we'll...we provided both in our report and in this presentation.

So, how was mortality in the field estimated? Christopher Salice yesterday noted that when they...they applied the DREAP formula to try to estimate how much mortality occurred in those treated fields. That formula was deemed inappropriate by the

study authors, and there's a rationale provided in the field study reports.

And it's primarily due to the fact that the birds were in pre-migratory phase. They don't have high site fidelity at the time that these studies were conducted, and so, the DREAP formula really doesn't work in that situation.

So, we took a different approach, as...we took the approach suggested by the study authors where we determined the number of live birds observed per dead bird found. And we convert that to percent mortality. We do that for each plot, and we did that for all birds across each plot, each field.

These calculations, again, are shown in gory detail in our assessment report. There's tables provided of all the raw data, and then all the formulas that were used to process the data are included in our report.

Unfortunately, the calculation that EPA used to calculate percent mortality using the DREAP formula have not been provided to us, and I don't believe they've been provided to the SAP. The first time we saw that was actually yesterday during the presentation.

So, that allowed us to estimate percent

mortality for treated plots and for control plots for both the corn and the alfalfa field studies.

So, what did we do with Liquid PARAM? We ran scenarios that replicated those field studies for each of our focal species. So, that's 1 pound of active ingredient per acre, foliar spray. And we determined percent mortality across all of our bird species. So, we combined the results for all of our focal bird species across 1000 fields, and those calculations are all shown in our report.

What were the results? On the x axis with the two crops, corn and alfalfa. The y axis is mortality per application expressed as percent going from zero to 50.

Here are the results, depending on how you calculate them for the field. Overall, there's very low mortality for both corn and alfalfa in the field, less than 1 percent no matter how you calculate it.

For corn, if you make no correction for pre-application or control mortality, then observed mortality was 0.88 percent of the birds. If you correct for only pre-application mortality, that drops somewhat, because some birds did die pre-application. So, that's 0.69 percent, and in this case, control mortality was so low for corn that it doesn't change

when you correct for that.

For alfalfa, even lower mortality, 0.3 percent if you don't correct for control or pre-application mortality, 0.26 percent if you just correct for pre-application mortality, and it actually drops to a negative value if you correct for control mortality, the reason being is that, in this case, control mortality exceeded what was observed in the treated plots.

And I would take that with a heavy grain of salt, because chlorpyriphos was used in these control plots. So, it's a reasonable argument to not consider that correction for control mortality for alfalfa in particular.

What were the results for Liquid PARAM? For corn, we predicted 0.78 percent mortality across all the focal bird species. A very low value. Certainly comparable to what was observed in the field, depending on which correction you want to compare to.

And for alfalfa, 0.33 percent. Again, pretty comparable to the field.

Apparently, having a perfect model like this is a bad thing. Had we not replicated observed mortality very well, I'm sure we would have been criticized for that, but it's interesting to see that

we're criticized for good performance. But, anyhow, I take that with a grain of salt.

There...there was...this is only two field studies. The model performed pretty well. We weren't expecting, actually, this close a match. What we were hoping for was that it was in the ball park, and I think that's all you should take away from this. Let's get realistic. There are issues associated with the field studies.

So, all we can really say is that Liquid PARAM is certainly within the ball park of what you would observe in field studies. How about TIM Version 1?

Dramatically different predictions. With the same scenarios that we ran in Liquid PARAM, using the corn scenario, TIM Version 1 predicts 40 percent mortality across all the bird species that would use treated fields and 39 percent for alfalfa. That is a mass mortality event, and there is no conceivable way that a study as well conducted as these two studies were that that kind of mortality would have been missed in this kind of controlled field study.

I should note that waterfowl were not present in the area during the conduct of the alfalfa field study, so we do not include alfalfa in our model

simulations, nor did we include them in the TIM Version 1 simulations, and that's exactly analogous to what EPA did when they did their alfalfa analyses.

Okay, so that's the model itself, and now I want to talk about the risk results that we got.

To help communicate risk, because risk curves are kind of a gnarly beast to communicate, we developed a risk categorization scheme. So, we took each of our outputs, and we categorized them as to whether they were de minimis, mild, intermediate, or high risk. This was strictly a communication tool, not meant to imply anything with regard to decision making.

So, how did we come up with those risk categories? If you read through the ecological literature, there's a general understanding that effects of less than 10 percent are unlikely to be ecologically significant to a low pop...local population. That...that statement would not include threatened and endangered species.

And it's because of things like density dependence. There's a certain amount of mortality that local populations can observe...can absorb without affecting overall abundance of the population.

Glenn Sutor, in a review of the literature, concluded that effects of 20 percent or less are

generally acceptable in EPA regula...regulatory practice. So, we kind of started with those two concepts and...and started to think about how we would categorize risk.

And what we figured is if there was a low probability of...of 10 percent or greater effect, so an effect that's, you know, unlikely to...to affect the local population, if there's only a low probability of exceeding that, then that's low risk. So, in our analysis, we say if there was a less than 20 percent probability of a 10 percent or greater effect, that was low risk.

On the other hand, if there was a high probability, a greater than 50 percent probability of a 20 percent or greater effect, the threshold that Glenn Sutor refers to, we...we considered that high risk.

At any values between those two, we consider it intermediate risk, and then we further came up with something called de minimis risk, and that's a situation where you have a very low probability, less than 5 percent probability, of even a small effect, a 5 percent or greater effect.

And so, that's...that's kind of the...there's more thinking to it than that, but that's just boiled down to the simple situation that we came up with.

Now, we kind of extended this a little bit further. If you take those probabilities and in magnitude effect and multiply them together, you get something called a risk product. So, if you take 20 percent probability times 10 percent effect or greater, that's a...what we call a risk product of 2. If you take the 50 percent probability of 20 percent effect, that's a risk product of 10. And we can do that for the other categories as well.

And so, what we did is we defined these regions, and I'll show them, these regions that describe high risk, intermediate risk, low risk and de minimis risk using these risk products, and I'll show you what that means.

So, on the x axis, we have percent mortality. On the y axis is exceedence probability, and that whole area to the right and above that blue line, if we get a risk curve that goes into that area, that's high risk. That's a high probability of a major mortality event.

That risk product of 10 that I alluded to as the criterion for high risk is what is used to calculate this line. So, 100 percent probability of 10 percent effect, that's a risk product of 10, just as 100 percent probability of 10 percent effect is a risk product of 10, and if you do that at multiple points

along the line, you have this line here equal to a risk product of 10.

Do that for the line dividing intermediate and low risk, that would be a risk product of 2, and so on for low and de minimis risk.

So, any risk curve that crossed into here is high risk. Any risk curve that crossed into here is intermediate risk, and any risk curve that was in here is low risk, and any curve that had a very low probability of even minor effects so it hugged the axes, was categorized as de minimis risk. Again, this is just a communication tool.

So now, I'm going to get into our actual results. We looked at a number of use patterns associated with the six crops that we were interested in, the five that the registrant would like to have on the amended label as well as alfalfa which has been removed from that label. We looked at the application methods that were on...on the label, the maximum single application rate, and we applied it at the maximum number of applications allowed according to the label.

For each of those crops, we identified a number of focal species. These are species from field studies that have been observed in these crops and using these fields quite frequently. So, these are the

birds that you would expect to be most at risk in treated fields.

Some of these overlap with what EPA considers in TIM Version 1. The ones that are in bold italic are species that we've added to Liquid PARAM.

Very...taken a lot of results, and there's...there's every single risk curve that we developed and all the statistics and assoc...associated with those risk curves are all presented in our appendices, but boiling it down to a couple of really simple slides, here are the results. We looked at, all together, 208 scenarios. That's combinations of use patterns times focal species, and in the case of...cases where we did not have species-specific toxicity data, three different sensitivities.

We found de minimis risk, very low risk, in other words, in 166 of our 208 scenarios, and if you go back and look at the numbers, de minimis risk turned out to range from 99.4 percent to 100 percent survival.

We found low risk for 27 of our 208 scenarios that we looked at. And, again, if you go back to the...the data that was generated to put those risk curves together, that indicates 95.2 to 99.5 percent survival, just to give you an intuitive feel of what low risk means.

Intermediate risk was found in 10 of 208 scenarios. That's associated with 77.4 to 95 percent survival. And we found high risk for 5 of 208 scenarios which range from almost complete mortality to 65.8 percent survival. All of the high risk scenarios were associated with gorge feeding waterfowl in alfalfa.

So, Christopher Salice's statement that Liquid PARAM predicts no risk for modeled uses except waterfowl on alfalfa, that was obviously false. That was a statement that was provide yesterday.

Clearly, in the vast majority of modeled scenarios, we did find risk, even if it was minor. No risk would imply 100 percent survival for the entire use pattern.

A little bit more discussion of risk results. For non-waterfowl species which are mostly passerines, de minimis risk in all scenarios if the species have low...are assumed to have low or median sensitivity to liquid carbofuran, generally de minimis or low risk if species have high sensitivity to liquid carbofuran, but we did find intermediate risk for highly sensitive species if they forage extensively in potato fields which has the highest application rate for the product.

Waterfowl species in alfalfa is quite a

different scenario. Alfalfa is...is actually attractive to waterfowl. Waterfowl will actually feed directly on alfalfa which is different from other crops. And during migration, they have the potential to gorge feed, because they...they've been undergoing a high energy activity, flying, for a number of hours, and so, they gorge feed quite often when they alight on fields.

So, to account for this behavior, we assume gorge feeding for waterfowl species in alfalfa, and we further assumed 100 percent foraging time on treated fields. And when you make those assumptions, American widgeon are at high risk regardless of sensitivity, and Canada goose are at high risk if they have high or median sensitivity, intermediate risk otherwise.

Now, I think there's a little context needed here. For a waterfowl species to actually gorge feed in a treated field...this is actually a fairly infrequent event, because the fields would actually have to be in the flyways. They would have to be treated at the time that the birds are migrating through the area, and in fact, most of the time, by the time treatment occurs in alfalfa, the waterfowl species are much further to the north, but, occasionally, it does happen, and so we wanted to look at this scenario.

So, it's a relatively infrequent event is the message I want to say, but when all the things align, flyways are in the area where there are treated fields and the birds happen to land on treated fields shortly after application, there can be very high mortality, according to the model.

Let's look at a typical result. Here are the risk categories shown here for the...that separate high, intermediate, low, and de minimis risk. The example being presented here is killdeer in corn. Post-emergent foliar spray. Application rate of 1 pound of active ingredient per acre. So, what do the risk curves look like?

Here's the result if we assume that killdeer are a sensitive species, a 5th percent...a 5th percentile species. That's that red line that just came across here. And how you read this is there's about just less than 20 percent probability that mortality will be 5 percent or greater.

Whereas if you go over to, say, 30 percent mortality and you read back across here, that would be roughly about an 8 percent probability of 30 percent or greater mortality for killdeer in treated fields. And that's how you read one of these curves.

Because this risk curve, at least part of it,

is between this line here and this line here, that's the low risk area. So, this outcome would be categorized as low risk.

If we assume...if we assume that killdeer are a median sensitivity...we really don't know what their sensitivity is...here is the result, and, basically, that's a de minimis risk result. There's a very low probability of any mortality to killdeer in corn.

And, as you would expect, same sort of result if they're a tolerant species. That's a green line here. It's actually right underneath that blue line. You can't see it here. Okay?

So, that's an example of what results look like for a lot of our passerine bird species in crops like corn, cotton. Potatoes, sometimes the curves are higher than that, and if you look at the risk curves for waterfowl gorge feeding in alfalfa, they would be up here. They would be up in this high risk area, very high probability of severe mortality.

All those risk curves are presented in our report.

In the ab...as has become clear, I think, in the absence of species-specific toxicity data, the uncertainty regarding predicted mortality can be quite high. This point was made yesterday, and we certainly

concur.

To get at that issue, what EFED did in their 2005 report is they used their mean mortality estimates for the entire species complex...so that's all the focal species they looked at...times the three sensitivities to estimate what risk might be for the community...at the community level for birds that forage in treated fields. This is a...a very interesting approach, and we repeated these analyses for each of the exposure scenarios that we did.

Here's an example output. This is banded application on corn, 1 pound of active ingredient per acre. On the x axis is bird mortality going from zero to 100 percent. And on the y axis, we have percent species affected.

We did the analysis for TIM Version 1. This is the exact same result that EPA got and presented in their report, and we did the analogous simulations in Liquid PARAM. That's the blue curve.

So, let's get an idea of what this really means. If you look at the predictions from TIM Version 1, it's predicted that for this use pattern, 67 percent of the species would have greater than zero percent mortality.

28 percent of the species would have at least

27 percent mortality. So, if you go to the x axis here, at 27 percent, go up and read across to the y axis. That's a 28 percent of species would have at least 27 percent mortality.

And for the species at greatest risk, they would experience 86 percent mortality.

In Liquid PARAM, the vast majority of species would not be predicted to have any mortality from this scenario, and the species at greatest risk would experience 3.3 percent mortality. Obviously, dramatic differences between the two models, and I would state that this kind of curve that you're seeing for a very common application scenario in recent decades is a mass mortality event.

This is even more dramatic for foliar spray on corn, again, a common use pattern of carbofuran in recent decades. Here, you're seeing greater than 50 percent of the species experiencing more than 50 percent mortality. That is a massive bird kill with some bird species experiencing as high as 95 or even 100 percent mortality. Quite...quite a bit lower predictions in Liquid PARAM.

Based on the evaluation of model performance that we did for TIM Version 1 and Liquid PARAM, we would argue that TIM Version 1 dramatically

overestimates risk. And why is that the case?

I think time step is a major reason, because time step reduces...with a longer time step like 12 hours, that reduces the influence of rapid processes such as metabolism and degradation in the field.

The rate of metabolism that was used by EPA in their assessment was based on whole body elimination. We used a value based on recovery of brain...from brain acetylcholinesterase inhibition, a much faster number..

Avoidance was not included in TIM Version 1. It was in Liquid PARAM. Dietary matrix influence was not included in TIM Version 1, but it was included in Liquid PARAM.

And there are a number of other possible explanatory variables as well, because we did do dietary residues quite differently, proportion time foraging in the field and so on quite differently.

And even in TIM Version 2.0 which does have a better time step, a quicker time step, 1 hour, because they use quite different daily foraging behavior patterns, something approaching gorge feeding, I would argue that that also leads to higher predictions of mortality than you would see with Liquid PARAM which has the same time step.

So, those are some of the reasons I believe that TIM Version 1 and 2.0 over-predict risk.

A little bit...a little note on how we dealt with uncertainty in Liquid PARAM. I think it's apparent to anybody who's...who's been involved with avian risk assessment of pesticides, there is limited information for a number of the input parameters that...that we need to...to estimate exposure and risk. As I mentioned before, direct measures of the proportion of diet obtained from treated fields by individual birds is just not available for North American bird species, at least the ones we're interested in.

Toxicity data are not available for most focal species, and what toxicity data are available simulate gorge feeding, that bolus dose placed in the crop of the bird or the esophagus of the bird. That is not the typical feeding pattern in...in the field. And no matter which model you're considering, TIM Version 1, 2.0, 2.1 or Liquid PARAM, they're affected by these sources of uncertainty. I think we need to be up front about that.

Like I said, I hope five, ten years from now, we're going to have better data and improved models as a result of that.

In this example when information was limited, we took a number of steps to deal with that. The preferred approach was to have studies conducted to fill the data gaps, and you heard about those studies from Keith.

To account for uncertainty where possible, so, for example, the allometric model that was used for food metabolic rate, that allometric model was a regression model. It has an error term. We incorporated that error term in our assessment and in our model which was not done in TIM Version 1.

We partitioned variation between individuals for...for dietary residues and proportion time foraging in the field or between fields and within fields.

And failing all that, we used conservative assumptions. For example, for brain...for recovery from brain acetylcholinesterase inhibition, we used the highest half-life that was from that study. You could, in a refinement of the model, actually put the dose dependence relationship between half-life and dose and actually refine the model from there. That line only had three points on it, so we're a little uneasy about that and went with a conservative assumption instead, but there's no reason why you couldn't refine the model to...to deal with that dose response relationship.

Okay, that...that's the part of my talk to do with Liquid PARAM. Talk very briefly about other lines of evidence. Yesterday, you heard from Melissa Panger a list of deficiencies that have been associated with state monitoring studies. There have been a number of monitoring studies conducted by states where they go in and look for dead birds following application of carbofuran.

And there are deficiencies in a lot of the monitoring studies, and we acknowledge that. For example, the use of ATVs to go look for carcasses is obviously an inappropriate way to go look for dead birds. You would...you would miss a lot of dead birds.

But there were some studies that were well conducted. There was kind of a broad brush used approach yesterday, you know, oh, there was all these deficiencies, and they apply to all state monitoring studies. Well, that isn't true. It applies to some, but there are some studies that have been well conducted.

These studies have been reviewed by Smith, 1997. That report is in the public docket. It's quite an extensive review of all the state monitoring studies. And I'm just going to touch on a couple of these studies that were better conducted studies and

talk a little bit about the results that they got.

So, California, they undertook state monitoring studies in 1995 and 1996. Searches were conducted by foot of the perimeter and interior of the field. All together, 153 miles were searched following application of carbofuran, liquid carbofuran. Those searches were conducted in zero to 3 days post application. Searches included census counts for each of the species observed in and around the fields.

I should further note that the searches that are involved in that study were actually trained searchers. They were trained by the California Department of Fish and Game, I think. I just have the abbreviation in front of me, but anyway, they were trained by the state agency.

And what they found was they didn't find any mortalities due to carbofuran in those 153 miles that they searched. They did find 7 birds which...dead birds which, when you did the residue analysis, it was pretty clear that it was an organophosphate that caused those mortalities. So, it wasn't a case of them missing dead birds. They did find dead birds. They just weren't due to carbofuran.

Oklahoma in 1995, 46 acres of edge and field were searched by foot 2 days after treatment. Again,

census counts. Again, zero mortalities due to carbofuran.

And just a clarification. In the RED report, EPA 1996, it's claimed that ATVs were used in those California searches. They were not.

Texas, I want to talk a little bit more about Texas, because Texas has probably done the most comprehensive state monitoring program for carbofuran. In 1995 and '96, they surveyed 697 linear miles of perimeter and edge habitat by foot 3 hours to 15 days post treatment. They didn't do counts or abundance determinations for each species of bird, but they did note presence/absence of species, and no dead birds were found.

1997, EPA requested that 30 acres be searched on 30 randomly selected sites, that these be done 24 and 48 hours post treatment, that the transects be 6 feet wide in areas of wildlife use which would be primarily the edge and border areas but also the field interiors, and that the searches be done by walk at less than 2 miles per hour. So, EPA had reviewed the profile. This is what they asked for.

To the extent that the state could, they complied with these requests. They search...all together, they searched 273 acres. They did so 48

hours post treatment, because they were not allowed to enter the field sooner than that. All together, 392 miles were searched at the pace requested by EPA. These searchers were also trained researchers. They were trained by state and federal wildlife agencies.

Numerous wild birds found in and around the fields, and these were censussed. Zero mortalities due to carbofuran.

Just to give you an idea of how intense these searches were, there actually was a mourning dove nest that was found in a treated cotton field. It was detected 2 days post treatment, so during the first search, and they actually went back repeatedly to find out how that nest fared. The eggs did hatch. The birds did fledge. That's...that's an ancillary comment. It's nothing about whether there's risk in this field or not. It just gives you an idea of how involved the searchers were in searching these fields.

A little bit about incidents. You heard a lot about incidents yesterday. What I've got here is a summary of the incident reports for liquid carbofuran 1998 to present. This is for birds. On the x axis are a number of categories from abuse/misuse, unknown, alfalfa, and then the five crops that are currently included on the amended label.

What has happened, if we look at number of dead birds, there has been a tremendous number of dead birds that have occurred due to misuse, and I'll come back to this in a little while, a few due...due to unknown use. There was a large number of birds killed in one incident for alfalfa, and then very few birds killed for the remaining crops...that have been killed on the remaining crops.

If you look at number of incidents, there are a large number of abuse and misuse incidents, a few unknown, one for alfalfa, one for corn, nothing for all the remaining crops.

The reason we picked this interval of 1998 to present is that reflects the current label. John, in his earlier presentation, noted that there were a number of label changes in 1997. The influence of granular product on incidents has been removed at this point. So, this is a...a more accurate picture of what might be occurring in this time frame.

A little bit about this number here, 31,048. At least 27,000 of those birds is due to one incident. And that incident was an Illinois baiting incident. The farmer actually was quite annoyed by all the birds that were foraging in his field. He took seed...grain, actually...treated it with undiluted furidan, and then

broadcast that over the field. It's hard to argue that that's a clear misuse, an off label use of the product. He was charged as a result.

So, 27,000 of those...those birds on there or more were due to that particular incident.

Also included in that bar there is a...the cauliflower...Colorado sunflower incident that you heard about yesterday, that complicated scenario that Melissa described. It was a large bird kill there. The reason we've moved it from an unknown to the misuse...yesterday, EPA had it in the unknown chara...category, and we have it in the abuse/misuse category...is because that grower entered a guilty plea with the Department of Justice January 3rd of this year, admitting to deliberate misuse of the product. It's called an off label use, and so, that does not apply. That incident is not an unknown; it is a misuse.

One other comment. You'll note here the value that there was 803 waterfowl birds that were killed in this one incident in alfalfa. In the figures presented yesterday, it was 1200 birds in this incident. I don't know where the discrepancy comes from. All I can say is that that value that we use here was based on a Freedom of Information request that

the registrant submitted to the EPA, and EPA provided this number to us as a result of that request. Otherwise, I can't explain the discrepancy.

A little bit about incidents in New York and California. As you remember...

DR. HEERINGA: Dr. Moore, if you could, try to push to wrap up in about ten minutes.

DR. MOORE: I am so close to wrapping up. Okay. Are we into lunch or...all right. You have no concept of time when you're up at the mike.

Very quickly, then, you noticed yesterday that the vast majority of incidents that have been reported by states since 1972 were in New York and California. There's a reason for that. 29 of the 38 incidents from New York State actually occurred in the city, and they represent a clear misuse, the baiting of pigeons.

California, 50 of the 111 incidents were related to application on grapes. That's a unique application method. Doesn't apply to any other crop, and as explained yesterday, it has since been mitigated.

So, I think that partly explains why there's a lot more incidents reported by New York and California compared to other inci...states.

So, to wrap up, which the chairman apparently wants me to do, some final conclusions. We believe, as a panel, an independent panel, that liquid carbofuran poses minor risks to the field birds that forage in treated row crop fields, such as corn, melons, potatoes, and so on. That gorge feeding waterfowl may be at high risk or...or intermediate risk in treated alfalfa fields if they happen to forage in those fields shortly after application.

We believe that the results from Liquid PARAM are at least consistent with controlled field studies, the results of field monitoring studies and incident reports.

And we would contend that it is unlikely that expert field researchers, trained searchers, farmers, growers' associations, government officials, and so on would have missed, over a long period of time, EPA's predicted mass mortalities associated with labeled uses of flowable carbofuran. That just seems very unlikely.

And so, if that's what's predicted by EPA with TIM Version 1 and subsequent versions, it suggests to us that there are issues with regard to model structure for TIM Versions 1 and 2.0 and 2.1, and so, we would argue that questions regarding model structure are critical in considering the risk of flowable

carbofuran to birds.

There no questions addressing model structure in your charge, and we would respectfully request that you, if you have time at least, to consider questions regarding model structure. Some possible questions to consider, are refinements to the model structure of TIM Version 1 required to adequately understand the risk posed by liquid carbofuran to birds?

Is it better to ignore critical, albeit uncertain, variables or incorporate the available knowledge about the variables? And the reason we pose that question is the EPA had a number of questions about the avoidance study, the acetylcholinesterase study, and the dietary matrix study. They noted that there's uncertainty about that, and so, rather than deal with that uncertainty in...in the confines of their model, they would rather not include it in their model at all.

I'm reminded of a famous quote by Charles Babbage, errors using inadequate data are much less than those using no data at all. We do have data here, obviously, and...this is my...my own further statement...using adequate data would be even better. We obviously believe that the data from the registrant's submitted studies are adequate, even if

there are uncertainties.

And, really, if you think about it, all variables in the avian model are uncertain, and some of them are really uncertain, such as proportion time foraging in the field, and those variables were included in TIM Version 1, 2.0, and 2.1, so that argument doesn't hold for excluding some of the variables that we've addressed in our studies.

We would like to see what the panel thinks about Liquid PARAM. Is it a better model for assessing avian risk? And as sort of a final grand question, which of the EPA and registrant assessments represents the best available science for characterizing the risk of liquid carbofuran to birds?

We know you have a packed agenda with the charge questions you already have, but we do hope that there is time to address some of these more fundamental questions regarding model structure.

And I thank you for your time and attention.

DR. HEERINGA: Thank you very much, Dr. Moore and Dr. Solomon as well. A very detailed and comprehensive presentation.

I would like to turn to the panel...we're going to break for lunch shortly, but...to see if there are several key questions, particularly for those of

you who have questions where you think that the...in regards to the environmental exposure and avian risk assessments. Yes, Dr. Clark?

DR. CLARK: This gets to the field studies' differences. In terms of the detection efficiency and observer reliability, were those estimates included in the model? Were they known?

DR. MOORE: They were included in the...sorry, Dwayne Moore. Those estimates of carcass search efficiency and...and loss rates from the fields were done by the study authors for each plot. They provided that data in those field reports, and we used that information, then, in making our calculations regarding percent mortality. We provided the raw data as well as the corrections.

DR. CLARK: As a follow-up, then, in terms of the population estimates as well in terms of the authors were estimating what the population numbers were in the area, were the same sorts of reliability estimates and...calculated for that as well?

DR. MOORE: I'm going to turn this over to Lou Best.

DR. CLARK: And detection efficiencies.

DR. MOORE: Yeah, Lou Best is actually more of an expert, so I'll let him answer that

question.

DR. BEST: No, as was stated, the...oh, excuse me. I'm Lou Best. As was stated, they did make a correction for disappearance rate and...and efficiency searching for the carcass. There was no such correction made for bird observations during the surveys which merely means that those bird counts were actually under-representative of the total bird community that was there, because no adjustment was made for detectability of the birds.

DR. HEERINGA: Dr. MacDonald, then Dr. McCarty.

Just for for the panel members, too...Ken asked for this question...I expect this period of questioning to continue after lunch for a short period of time, so you don't have to rush in, but I want to take the proper time.

DR. MACDONALD: Yeah, I'd just like to comment. I think we've had some extremely good presentations, and I'm very impressed with the description of the...the model, the Liquid PARAM, but I think it's impossible for us to say which model is good science, because we haven't had peer review of the Liquid PARAM model. We haven't had EPA review of it. We just have to take your word that it works as...as

you describe.

DR. MOORE: Dwayne Moore. Yeah, I agree. I mean, if it had gone to peer review, I think that adds credibility. No doubt about it.

What we have provided, though, is a very detailed description of the model and all of its inputs. Every calculation was described in our report, and we do have a number of avian experts around the table who have experience. And so, I think the information is there to actually do that peer review that you think is important. And I agree it's important.

DR. HEERINGA: Dr. McCarty?

DR. MCCARTY: Two quick questions. One, a quick follow-up on the bird observations and the census of what's out there. Were those unlimited radius counts that you did?

DR. BEST: In the alfalfa study, they were transect counts. I can't remember...

DR. MCCARTY: Do you know the distance?

DR. BEST: ...the width, and I would have to go back to the studies, but the studies do describe the width of the transects and also the length of the transects. And they...what they did is made the surveys on the perimeter of the field, so they were

simultaneously counting birds on the field perimeter as well as birds in the field edge.

DR. MCCARTY: But you don't remember the width and...

DR. BEST: I haven't recently looked at the study, no, but it is in the report.

DR. MCCARTY: And we don't...

DR. MOORE: We can get that information for you after lunch.

DR. BEST: We can get that information for you.

DR. MCCARTY: Okay, that would be good.

The second quick question is on page 18, talking about the...the even daily feeding rates or feeding rates through the day. I know some of those studies, and I know at least some of them involved feeding nestlings, and I'm wondering if the estimates you...you use partition out the adults feeding themselves versus adults going out foraging and bringing food to the nestlings, because, of course, the models, as far as I know, ignore nestlings, and they're just focused on adults.

Do you know...were you able to partition out how the distribution of adults feeding themselves looked?

DR. MOORE: Dwayne Moore. In the model, no. As...as I understand it, those observations were just counts of how many trips the bird took away from the nest and returned, but I'll let Lou expand on that. He's...he was involved with some of those studies.

DR. BEST: That's correct. They were simply frequency counts of...of bird forays from the nest and then returning to the nest to feed the nestlings. The assumption there would be that the foraging pattern of adults would...would mirror the foraging pattern for the young which I don't believe is an unreasonable assumption in terms of the frequency of forays, because much of the time they're...they're going to return to the nest they're spending brooding. They would be actually at the nest itself. So, they have to feed at the same time they...they go on a foray to seek food for their young.

DR. HEERINGA: Yes, Dr. McCarty?

DR. MCCARTY: Would that apply, say, to, then, you know, a recently arrived migrant in May, small passerine crashing down in a fence row or something or a...a shore bird, say, a golden flubber during migration in early May in a cornfield?

DR. BEST: Lou Best again. That's certainly a valid question. There is, I think, an

important distinction to be made between waterfowl and gallinaceous birds like bobwhite quail and passerines in the fact that the passerines do not have a crop. They do not have a storage organ which necessitates them feeding more frequently throughout the day. So, the comparison is confounded by that.

DR. HEERINGA: Dr. Sample and Dr. Sparling have questions, but if...I'm going to ask them to hold those till after the lunch.

Before we do break for lunch, I...I want to just give you my synopsis of how things are moving along. Clearly, we are behind schedule, and my deepest apologies to public presenters who are here for a short period of time to make their...their statements and their presentations, but we have to stay with the order of the agenda. It is floating, and these discussions are absolutely critical to the scientific review.

So, my apologies, but I am going to proceed with the careful review of this material.

Before we break for a one-hour lunch...I want everybody back at 1:30...the Designated Federal Official, Dr. Sharlene Matten, has a few comments to make.

DR. MATTEN: Actually, Dr. Heeringa took part of what I was going to say. The public

commenters, I understand that one or two may have to fly back. If you would let me know what time you need to fly back, with some adjustments with other public speakers, we might...we certainly don't want you to have to pay $1000 to reschedule your flight. That's not what we intended. While we're floating, we are certainly cognizant of people's time, and if you could come see me if you have a 5:00 o'clock flight or 6:00 or 7:00, we may be able to make some adjustments.

Our usual process is to take the oral comment requests in the order in which they come to me, and so, if there's some flight concerns, please let me know, and we'll...Dr. Heeringa and I will...we'll talk about it and we'll let...because FMC has several more hours of presentations.

The other note I wanted to make is if you've come to me with your scheduled time, please try during...at least during the presentation to more or less stick to the time in which you've at least given me previously.

Thanks.

DR. HEERINGA: Thank you, everybody, and we will break for lunch now. Again, we'll resume at 1:30.

(WHEREUPON, Session B was concluded and a luncheon

recess was taken.)

DR. HEERINGA: As soon as we can get a Designated Federal Official, we'll get under way. We're still waiting a Designated Federal Official. I can't start without either Sharlene or Steve. Can I deputize somebody? I don't know.

In the process, we have entered a period of public comment, and we are receiving presentations by expert panels that have been assembled by the registrant and have conducted various research and developmentals and exploration activities. We have heard the presentation on the avian risk assessment additi...supplemental studies and actual modeling efforts with Liquid PARAM, and we are at a point now where the panel is addressing questions of clarification to...to the presenters on this topic.

Dr. Matten, the DFO, reminded me, too, we want to make sure we stay within reasonable time constraints on all of our comments. That includes both presentations and our questions, but, again, I'm going to balance that to make sure that we get full development and exploration on...on these issues. So, I'll try to manage that accordingly, but you know where I'm going with things.

So, let's...at this point, let's return to

questions of clarification.

DR. MOORE: All right, Dr. Heeringa, we do have an answer to one of the questions posed before.

DR. HEERINGA: Yes, Dr. Moore, why don't you provide that?

DR. MOORE: Well, actually, Lou Best will provide an answer to that. That was with regards to the field studies.

DR. BEST: There...there were some questions asked about the...the length and width of the...the nature of the transects. For the alfalfa study, the transect width in the middle of the field was 50 meters wide on either side of the midline of the transect. On the field edge, it was 25 meters on either side of the midline. They were fixed width transects.

In the cornfield study, it was a bit different there. They had a variable width transect for the edge habitat, depending upon the extent of that edge habitat, because they were dealing with, I think, fence rows and so forth, and because of the difficulty in making observations in tall corn, they actually did their surveys from platforms. They were positioned...they had two per field. They had three surveys per week, and the radius that they surveyed

was, let's see, I think it was a 50-foot radius from those...50-yard radius from those platforms.

DR. MCCARTY: So, would I interpret from that the variable width on the edge means they tried to...they just count birds in what they were defining as edge?

DR. BEST: Right. What you typically will find is...is something like a fence row or some strip cover along the edge, and, basically, the width is dictated by the width of that particular strip cover.

DR. HEERINGA: Thank you very much, Dr. Best.

Picking up where we left off before our lunch break, I think Dr. Sample, Brad Sample, had a question.

DR. SAMPLE: Yeah, I was looking through...or in the presentation, you were talking about the application of the...a factor to adjust for food matrix. I noticed that you used a value of, I guess it was, 3.8.

DR. MOORE: Yes.

DR. SAMPLE: And there were...that was based on the quail study. There was also the data that were based on the mallards which was a lower value, a value of about 2, and I notice you did not use that in

your model and did not discuss it. Is there a particular reason, and how does that...how did that affect your modeling results?

DR. MOORE: That value of 2 for mallards was the value devised by EPA. In our analysis of the mallard data...and this is in our...our report as well...we calculated a worst case lowest value for the mallard study for the adjustment factor and a best case, and it...that range was from 2 to 4.6, depending on what assumptions you made about slope of the curve and so on, the probable slope. And that 2 to 4.6 actually brackets 3.8 in the middle. So, we felt that 3.8 was a reasonable factor to apply for all of our analyses.

Obviously, that's a...an uncertainty as to whether the results for two bird species apply to all other focal species, but as...as a reasonable estimate for both bobwhite quail and mallards, around the 3.8.

DR. SAMPLE: And you include that parameter as a...as a fixed value?

DR. MOORE: We did, and honestly, I think if we had enough to actually put a distribution around that, if we had more species...I know where you're going with that...I think we would treat that as an uncertainty as well.

DR. HEERINGA: Dr. Sparling had a question.

DR. SPARLING: Actually, if I could, I've got several questions, but I'm going to ask two, if I could.

DR. HEERINGA: Certainly.

DR. SPARLING: Okay. The first question is with regards to the food avoidance study. In the Liquid PARAM model, did you try to examine what the effects would be if you did not have food aversion going on there?

DR. MOORE: Yes, we did. In our sensitivity analyses, we ran set exposure scenarios. There's two of them, a high number and a low number scenario, and we ran them with avoidance turned off and with avoidance turned on, and it makes quite a bit of difference.

DR. SPARLING: And so, with avoidance turned off, there would be substantially more mor...mortality?

DR. MOORE: Yes, there would be.

DR. SPARLING: Okay. The second question, then, deals with the...and I think this is might...might be a follow-up on Dr. Sample's. In your studies, your extra studies that you submitted, you

indicated that the aqueous toxicity for the carbofuran was inaccurate on a bolus, that it was far more toxic than it was in a food bolus.

DR. MOORE: Mm-hmm.

DR. SPARLING: Okay. At the same time, it's my understanding in Liquid PARAM, you're able to model uptake or exposure from puddles?

DR. MOORE: We...in the...Dwayne Moore. In Liquid PARAM, you have options whether to...for drinking water scenario whether to do puddles day of application, puddles day after, or dew only throughout. For the results that we presented in our risk characterization, it was dew only, and that was to mirror exactly what was done by EPA in their assessment report. So, there was a dew only drinking water source in the...in our models.

DR. SPARLING: Okay. And then, when you looked at the effects and you made your decision yes, there was an effect or no, there wasn't an effect, was that based on food bolus LD50 or the aqueous LD50 or neither?

DR. MOORE: It would be based on the food bolus. So, what essentially, you're...I think, if I know where you're going...the dose response curves were all moved three-fold to the right to account for

dietary matrix exposure, and we did not adjust that for the drinking water part that would be coming in.

So, there's two dietary...or two routes of exposure. There's a dietary, and there's an assumption of dew.

Computationally, it would have been...I don't even know how you would do it. It would be very difficult to have...adjust that dose response curve for how much they were getting from drinking water versus diet. It would be an interesting exercise, albeit a difficult one.

But what we found was that the contribution that was coming from the dew drinking water sources was relatively minor, and this...this is corroborated by EPA in their assessment. They found that that source of exposure was relatively minor.

So, as our interim solution, I guess, we just simply went with the dose response curve adjusted for the dietary matrix.

DR. SPARLING: Okay. And one other question. This is going...going right back to what I...my first question. You said there was a considerable difference between the food avoidance calculation on mortality and without the food avoidance. Are we talking about an order of magnitude?

Are we talking about a two-fold? Can you give me a ball park figure?

DR. MOORE: I can give you a ball park figure. Be easier if I can use the graph for you. Give me two seconds. Almost there.

Okay, for horned larks which is a high exposure scenario, if you look at...at the results, assuming high sensitivity for that species, we would have predicted about 50 percent mortality if you do not account for avoidance. If you account for avoidance, assuming a 1-hour time lag in response, that drops down to about 14 percent predicted mortality, and it...if it were instantaneous, which it isn't, it would drop down to just a few percent.

That's our high exposure scenario assuming high sensitivity. If you assume median sensitivity or low sensitivity, it really doesn't matter, very low mortality, and if you do a low exposure scenario, avoidance...turning avoidance on or off doesn't really matter, obviously. Very low predicted mortality.

So, it's really just in a high exposure scenario with a bird species that gorges in the field a lot that it can make that sort of two and a half-fold, three-fold difference.

DR. SPARLING: Thank you.

DR. MOORE: And that's on, for anybody looking at it, it's page 118 of the report, Moore, et.al., 2007.

DR. HEERINGA: Thank you, Dr. Moore and Dr. Sparling. Dr. Clark?

DR. CLARK: It's Larry Clark. I'm just trying to get some clarification on the food avoidance studies, so...I don't know if you had all this information. So, how long were the...the birds down once they were exposed to their initial dose, inactive?

DR. MOORE: I think that's probably a question for Larry, Larry Brewer.

DR. BREWER: Larry Brewer. In the food avoidance study, we didn't have any birds that showed any signs of exposure.

DR. CLARK: Okay. And...and then, two other very simple questions is, were these studies run over a standard work week? So, did they start on a Monday and proceed through the Friday?

DR. BREWER: Not necessarily, no. Our lab runs all week long, and there's someone there every day of the week and usually a team of people.

DR. CLARK: Okay. I'm just trying to understand, for example, the...you have a total daily feed consumption data which is the...the food intake

adjusted for body weight over timer, and the controls show a pattern as well. Were the birds visually isolated?

DR. BREWER: From each other. I think probably what we saw in that little pattern that you saw in the control of the offering is a...is something we see in caged birds quite often. When you initiate a study, there's a substantial amount of activity, and it...it has an influence on the birds. It...it...in the form of stress. In a few days, they...they get used to...especially ducks. They get used to your patterns. They relax a little bit. They become more...more likely to...to consume normal amounts of food, and so you'll see that pattern.

And since it did happen in the controls, everything we did with regard to comparisons, I'd say, was back to the control, and so we felt that it was not an issue.

DR. CLARK: Thank you.

DR. HEERINGA: Dr. Montgomery?

DR. MONTGOMERY: Cheryl Montgomery. I'd like to follow up on the slide number 10 that's titled Appropriately Conducted Study. I believe Dr. Solomon presented this information. It says here there's no learning of location of contaminated food. Feeder was

switched each day.

And I was wondering if...I don't know if you were present yesterday or not, but the EPA put up a right and left side preference feeding for the birds, and I was wondering if you would be willing to comment on what EPA presented yesterday and how that reconciles with this, if it does.

DR. SOLOMON: Keith Solomon. If I just go to the next slide, perhaps, this illustrates the distribution of left and right side preferences in...in the birds in the study. This is all of the 70 birds that were used in the study, and we've color coded the...the various groups there, and we saw no...no bias towards one side or the other. And this data, obviously, we should probably do some more statistical analysis of it. Because of the time, we couldn't do that.

So, I will ask Larry Brewer who did the study to perhaps explain in a little bit more detail the points and how they were determined.

DR. MONTGOMERY: Well, may I just ask a clarification? Did you see the presentation that EPA made yesterday? I mean, I don't remember seeing your faces in the audience, so you know the slides I'm...I'm referring to, the bar graphs with the left and right?

DR. SOLOMON: Yeah...

DR. MONTGOMERY: For the preference there?

DR. SOLOMON: Keith Solomon again. The bar...the bar graphs probably refer to...well, some of them consistently favored the right side, and there were other animals that consistently favored the...the left side, and those were the graphs you saw yesterday which were the extreme ends of the...of the distribution, and the others were in between, and there was no apparent bias in...in a...in the study that they...and then, when we switched the feeders or we...when Larry's people switched the feeders every second day or every day they switched them, the...even though they preferred that feeder, they were then going to a feeder that was different than the one they had before.

So, we felt that controls...well, we believe that that controls as far as we...which we couldn't avoid, and Larry Brewer can probably give you a little more explanation on that.

DR. BREWER: Larry Brewer. For...for the purposes of this...of this slide, what this is, as we repeated earlier, everything on...on the right side shows...of the diagonal line shows birds that favored

the right side of the pen, and on the left side is the birds that favored the left side of the pen. And so, if you look at those, there's no real bias towards them doing one or the other, and in the...in the...the example given yesterday, the presenter said we picked an...an extreme example, and this is what we're hypothesizing about that extreme example.

And, again, because they would favor one side of the pen or the other...and I have some ideas why they do that. Some birds do. Some birds don't. I can get into that if you want, but because, every day, we switched the feeders from one side to the other containing fresh food versus contaminated food, they were getting the same exposure to...to the food in total number of hours throughout this day.

DR. MONTGOMERY: Was it fresh contaminated food?

DR. BREWER: No, it was fresh food, uncontaminated.

DR. MOORE: Right, uncontam...but it was fresh uncontaminated...

DR. BREWER: Every day.

DR. MONTGOMERY: And then, but you took the contaminated feed and switched it side to side, or did you put fresh contaminated feed?

DR. BREWER: They had fresh contaminated feed every morning.

DR. MONTGOMERY: And fresh feed every morning.

DR. BREWER: And fresh feed every morning.

DR. MONTGOMERY: Okay.

DR. BREWER: And the next day, they had the same thing in opposite positions.

DR. MONTGOMERY: Opposite sides, yes.

DR. BREWER: Yeah. And...and with regard to what makes a duck lean to one side or the other, we notice in mallards that they're kept...they're kept sexes separate prior to the study.

DR. MONTGOMERY: Mm-hmm.

DR. BREWER: When you put them together, even though they're in metal pens with metal dividers, the female mallard is the vocal leader in the group, and the males can hear the females next to them if they're totally randomly assigned to their cages, and then the treatments randomly assigned to that, but if they happen to be next to a female and they can hear her, they're going to spend more time on that side of the cage or if its' on the other side of the cage, and this does show a random propensity towards the sides of

the cage, and I really think that's the explanation.

DR. MONTGOMERY: Okay, thank you.

DR. HEERINGA: Just a...a note to everybody. I would like to terminate this questioning at about 2:15, because we...we have three other topics this afternoon to get to. So, we have about 15 or 20 minutes.

Dr. Edler and then Dr. Portier.

DR. EDLER: Just for a while on that...on that slide here. There is a time behind that. We have day 1 to 5, so which time actually this...does this figure belong to? Because I think we have a little bit of a problem here. We have that statements, we have the figures, and then we have the real data, and always see these three...these three fields very bounce...bounce around, and the figures, of course, cannot show always the data. Sometimes we need some more information.

DR. SOLOMON: Keith Solomon here, and I'll just...the...the raw data is available in the...on the CD that you've been supplied. We have all the figure from that study all available if you want them, and this...this is a mean value for the study that you see here. To put all of the individual days on here would have made it look somewhat uninterpretable.

I don't know if Dr. Brewer would prefer...would like to add.

DR. BREWER: Just that that...these values are the total feed consumed from both sides per bird for the...for the full exposure period.

DR. HEERINGA: At this point, Dr. Lu and then Dr. Portier. I know Dr. Portier has some detailed questions, but Dr. Lu.

DR. LU: Alex Lu. I have two fundamental questions regarding the Liquid PARAM model. So, you mentioned that you...you found there is a dose dependent half-life of recovery which struck me as a very shocking finding, because for all the pharmacokinetic o pharmacodynamics parameters that you estimate, the half-life is one of the few...it's not the only one...that's independent from the dose. The half-life effect by the route of administration will have an effect by which phase are you talking about, proportionately for inhalation, but in terms of dose dependence, it's very difficult for me to understand that there is a possibility that these two things will have relationship.

So, if you look at your slide 20 and 21, especially 20, the curve actually look really identical. I mean the previous one. Yes, the previous

one. This one. If you plot these three curves on the semi log paper and estimate a slope, that should give you the same number, and that slope will represent the half-life. So, I don't know how you calculate the half-life. There's no number that I can base this on.

So, that leads you to the problem on slide 21 which I don't know how you calculate that the half-life will lead to this linear relationship. Again, if you can comment on why the half-life is dose dependent.

And the second question or you can comment on this is that you using the half-life derived from the cholinesterase enzyme recovery in the model to estimate dose...to estimate body burden. It seems to me that you actually use the different and wrong parameter to try to come up with a different measurement outcome that has nothing to do with acetylcholinesterase enzyme.

It seems to me like...I mean, if you are going to use an estimate from the enzyme data, you are using some sort of pharmacodynamic model, but they're kind of like pairs, the...the parent compound and metabolite relationship, but I think the Agency presentation yesterday was talking about looking at the chemical in the environment or in the bird and they come up with the estimate half-life which...which I

think is reasonable, but in your approach, it struck me as somewhat very novel. So, if you can comment on this?

DR. SOLOMON: Dr. Lu, Keith Solomon. I will initially talk to that, and then Dr. Moore may add some comments to that. The...what we were looking at in this particular relationship here is...is not just cholinesterase. That's what they're measuring as an endpoint in vivo. So, we take these birds. We've gavage dosed them, and then we, at various times, we sacrifice them and measure the brain acetylcholinesterase.

So, what we're seeing is a combination of recovery of inhibited enzyme over time, but in addition to that, if there are any remnants of the initial dose of carbofuran still circulated in the body, they could inhibit newly released enzyme, and this would slow down the recovery rate.

So, it's a combination of cholinesterase and metabolism that we're seeing here, and I think that's why we see a slow recovery at higher dose. If I took this into a test tube, as I recall doing as a grad student, the recovery rate was always the same. It doesn't matter, because you're dealing with pure enzyme and no...no metabolism going on.

The...in that sense, we believe that this...because we're measuring the toxic endpoint...this is what kills the birds, is inhibition of cholinesterase. That is actually a very useful endpoint from the point of view of a risk assessment, because it is clearly related to mortality. It integrates, in this case, metabolism once the chemical is in the body and the recovery of the cholinesterase.

DR. LU: This is Alex Lu again. I think I disagree with your interpretation of this slide. If you look at...

DR. HEERINGA: Dr. Lu, we might want to...

DR. LU: Okay.

DR. HEERINGA: Unless it gets to a point of question. I mean, if it's really clarification on this, then I'll permit it. Otherwise...please, if you feel that you need clarification, but just for discussion at this point, I think we'd prefer to save that for later.

DR. SOLOMON: Well, I can pick this up, if that's permissible, Mr. Chairman, later on.

DR. HEERINGA: Yes, you certainly may talk with Dr. Lu and come back to us. Very quickly, to Dr. Grue and then to Dr. Portier.

DR. GRUE: Chris Grue, University of Washington. Was there a carrier used for...in the mallard study, the avoidance study?

DR. BREWER: Larry Brewer. In the avoidance, they were...were dosed in a...they were not...there...there was no carrier with regard to in the feed. They weren't dosed. They were, of course...it was a dietary.

DR. GRUE: That's what I'm saying. Did you use a carrier, though, in mixing the...the pesticide into the water...I mean, into the feed?

DR. BREWER: No, it was put in neat. It's a liquid. The product is liquid.

DR. GRUE: Okay. So, okay, so there's no...there's no carrier involved. Okay.

Maybe I'll just ask a couple other points of clarification?

DR. HEERINGA: Of course.

DR. GRUE: The time, the 1-hour time lag for the avoidance work...both of these are directed to Dr. Moore...and the 8-hour time step for the avoidance results, could you just clarify those two for us?

DR. MOORE: I'll do my best. The 1-hour time lag is the simple aspect of it. There are...because the birds aren't able to, as far as we

can tell, at field relevant concentrations, sense the compound in any way through taste or smell, there is not an immediate avoidance. As...as Keith talked about in his...his presentation, what happens is they feel symptoms from the exposure. They feel those symptoms within about half an hour. If you look at that graph, you'll see at half an hour is when...when the levels are lowest for acetylcholinesterase.

So, it's...I think it's our...our hypothesis is that the birds feel sick, they reduce their feeding, and then as the exposure is removed, they increase their feeding accordingly. So, that feeling of symptoms and reduction of food intake rate happens around half an hour.

So, because we have a 1-hour time step that's either zero or 1, we make it more conservative and said there's a 1-hour lag in the avoidance. It's certainly not immediate. If it was immediate, it would be a lower risk.

And what was the second?

DR. GRUE: Maybe just make a comment on this first point. I...I think it's important that you make a distinction between testing repellancy and a pesticide-induced anorexia, and what...what you're suggesting is that this is a pesticide-induced

anorexia.

DR. MOORE: Yes.

DR. GRUE: And...and that...the distinction is important, because it relates to the potential hazard in the field.

DR. MOORE: Yes.

DR. GRUE: And we can...we can talk about that more later.

The second clarification was the 8-hour time step from the avoidance results, then, into...into the model. I wasn't...I wasn't clear about that.

DR. MOORE: Sure. In the original study, food consumption was measured on a daily basis. As I understand it from talking with...with Larry Brewer, it's just not feasible to go in and measure on an hourly basis, because that amount of intervention would...would seriously disturb the birds. So, we have a daily consumption rate.

The model, however, has an hourly time step, so we had to get from those values in reduced food consumption expressed on a daily basis to the hourly time step. In the protocol for that study, it's...it's clear that they had an 8-hour daylight throughout the duration of that study. So, for mallards, it's a reasonable assumption that they fed over that 8-hour

period but not during the 16-hour dark period.

And so, basically what we did is we took the results expressed as daily divided by 8 to convert it to the hours that we have in the model. Is that an assumption? Absolutely, it's an assumption.

DR. GRUE: Okay, thank you.

DR. HEERINGA: Let's go to Dr. Portier now who, I think, has some questions on the model structure.

DR. PORTIER: Thank you. Slide 32. I have a few clarification on...on the methodology in the model. So, starting on the left, the initial concentrations in food and water, if I look at one field, one of your 1000 fields in the simulation, all 20 birds are going to basically receive a time series for food and a time series for water.

DR. MOORE: That's correct.

DR. PORTIER: In the slope of a K curve.

DR. MOORE: That's correct. Over time, they'll receive that.

DR. PORTIER: Again, for that same field, you've got one degradation rate for food and one for water. Right?

DR. MOORE: Actually, we have separate degradation rates for each of the parameters.

DR. PORTIER: Okay. So, for the...

DR. MOORE: For the grass, forage, seeds, and insects.

DR. PORTIER: So, when...when you put that together into concentrations in food and water over time, essentially, you've got, for each field, a time series.

DR. MOORE: That's correct.

DR. PORTIER: For each foray, a time series for water.

DR. MOORE: Yes.

DR. PORTIER: All right? Okay. So, you've got 1000 time series. So, that's that set. So, there is...

DR. MOORE: You know what?

DR. PORTIER: ...there's no bumpiness over time. They're pretty much...

DR. MOORE: Well, it's smooth and...

DR. PORTIER: Smooth curve. Okay. Foraging behavior is the one where I start to...to lose it right there.

DR. MOORE: Okay.

DR. PORTIER: In foraging behavior, it seems that there's two parts here. There's the how you take the total daily intake, the TDI, of a particular

bird, and distribute it over the 14 feeding hours of the day.

DR. MOORE: That's correct.

DR. PORTIER: So, that can be either for ducks, two on each side or...so, for a particular bird...well, we'll skip the field that's on the left, the bird's on the right. Right? For a particular bird, do all of 20 birds in that field have the same...of the same species have the same TDI distribution to the day?

DR. MOORE: Yes, they would have the exact same hourly intake rate per day.

DR. PORTIER: So, if we looked at your slide 36 there, slide 36, there would just be one for all 20 birds. Right?

DR. MOORE: That's correct.

DR. PORTIER: When I change to another field, same species of bird, do I have the same...

DR. MOORE: Same intake rate.

DR. PORTIER: Okay, so that's fixed for a bird.

DR. MOORE: That's correct.

DR. PORTIER: For a bird species. Right?

DR. MOORE: Yes.

DR. PORTIER: Okay. The other component, then, is the TDI for a bird. Is the TDI for a bird distributed, or is that fixed to body weight?

DR. MOORE: The TDI is distributed, and it's distributed based on the error term in the allometric models that we used to estimate a food metabolic rate.

DR. PORTIER: Okay. So, related to body weight or body size...

DR. MOORE: Body weight, that's correct.

DR. PORTIER: ...and you're looking at a distribution going in, and you distribute that. Okay. So, where does this discussion on slides 40 and 42 come in where you talk about field...

DR. MOORE: Ah, okay.

DR. PORTIER: ...distribution and dietary residues distribution?

DR. MOORE: Okay. You...you are completely clear in your understanding so far, so you did...

DR. PORTIER: Well, that...I mean, wasn't really sure.

DR. MOORE: That's great, and this...this is a hard...this is the hardest part. So, the birds get a certain portion of their daily diet

each hour of that distribution, but where they get it from still has to be decided. Do they get it from on the field, or do they get it from off the field?

And that's what this parameter does. This proportion time foraging in the field...

DR. PORTIER: So, there's a binomial proportion? Every hour, you flip a coin to decide if it's on or off the field, depending on the bird?

DR. MOORE: No, we...that's...that's a TIM Version 1 approach.

DR. PORTIER: Okay.

DR. MOORE: In our model, they can be on the field and off the field in the same hour. So, what we do is through this process of once we partition the variation between fields and within fields, we come up with a distribution that represents the range in proportion of time that they...each individual spends in the field, randomly draw that...from that distribution.

And that's that bottom chart there on slide 40, and what we have is for that particular field, we have a population for a group of 20 birds. Some will have...only spend a small amount of time foraging in the field, and those would be the bars right around 0.25, 0.35. Other birds in that group will spend a

large amount of time ever time step foraging in the field, and that would be to the right. Most of them seem to be around 0.65 to 0.75.

DR. PORTIER: So...so, the bird gets one draw, and they're a 0.25 bird...

DR. MOORE: That's a...

DR. PORTIER: ...and every hour, they're a 25 percent, then, in the field.

DR. MOORE: That's right. I mean, if we had data to distribute those variables, we would. We don't, but if you think about, particularly in the case of...of nesting passerines, they're going to have...they're going to make a lot of foraging trips per hour, and so, there will be some consistency from one time step to the next in where they spend their time foraging, so it's not a perfect...

DR. PORTIER: But that...so that fraction, the TDI, are going to be tied to the exposure that the bird actually gets in any particular hour?

DR. MOORE: That...that's independent of how much exposure they get.

DR. PORTIER: So, how does the exposure come in?

DR. MOORE: Well, once you have a concentration in all the dietary items...

DR. PORTIER: Right.

DR. MOORE: ...you know what the rate...the in...their intake rate and how much they get from the field. You have an hourly dose.

DR. PORTIER: Right.

DR. MOORE: The adjustment that's made for preceding dose is the avoidance function. So, we calculate an hourly dose, and then we look at how much they've accumulated so far and figure out how much they would reduce their food intake rate, and we reduce that current time step exposure accordingly. And that...that's how previous exposure factors into current exposure.

DR. PORTIER: Okay. The...the discussion on...what was it...figure 42 which talked about...I wasn't quite sure what that slide had to do with any of the other slides.

DR. MOORE: It was...it was really addressing a comment from EPA. As you noted, the concentrations, once we figure out the initial concentration in the field, decay, and we assume no intrafield variability. That...now, but EPA raised the concern that there is, of course, intrafield variability with dietary residues, and some of the coefficients of variation are listed on that slide, but

what I wanted to make the point of is that it's not that important once you account for bird foraging behavior.

The birds spatially and temporally average their exposures, because they are making multiple trips into the field, and so, all I was trying to do with this example, very simple example, is convey how the importance of variability in dietary residue within a field is reduced as a result of that spatial and temporal average.

DR. PORTIER: I understand. Slide...real quickly, please, slide 44 is your avoidance behavior curve. Now, if I was a...if I gave this to a student statistician, they would put a straight line through zero that would actually be sharper than your line and would have uncertainty of about plus or minus 25 percent at every dose. Right? In your...in your model, you're not using any of the uncertainty...

DR. MOORE: No.

DR. PORTIER: ...and you're using a curve which I don't believe fits the data.

DR. MOORE: That...that curve fits the data. The statistics are discussed in our...our report. It's a significant fit.

DR. PORTIER: Just not...

DR. MOORE: Yeah, is it messy? Absolutely, it's messy. I would very much like to, in a future iteration of the model, try to introduce the uncertainty into that. Computationally, it's difficult, because in each time step, you know, we have to randomly figure out how much draws from that...so, we figure out what the preceding dose was and then randomly draw from the distribution to account for the error and do that for each time step for each of 20,000 birds.

Even that is easy, but the problem here is this noise represents variation between birds, not between time steps within a bird. So, I would actually...what I would suppose is that this curve is different for every bird, and you would somehow have to account for that in a model.

That...that's just an ordinary way of saying computationally, it's a very difficult exercise. Conceptually, I completely agree with you.

DR. PORTIER: And the...the last one is 45. And on this one, I understand how you've created these three parallel lines, and...and I talked with my statistician colleague, and neither one of us believe that the...that the 05 or the 95 percent lines would be

exactly parallel if you...and then...and we're not going to argue this, and we can talk about this on the side, but I would have expected the line on the left to be tilted more. The slope would change.

Because what you're assuming here is you're just shifting the mean of the distribution. You're not affecting the slope at all, and the slope...the slope being the variants of the distribution. So, you're saying the variants of the distribution of lower percentiles is going to have the same variants as the distribution of the median, and that's just not going to be the case, but I understand how you did it.

DR. MOORE: Oh, I...I'm not sure I agree with that. What the variants of any one of those curves represents is variation in sensitivity of individuals within a bird species, and I'm not sure why I would expect variation in sensitivity to be different from...in a systematic way from one species to the next, but, you know, there's not enough data to answer that.

DR. PORTIER: I was going to say if you go back and you look at your slide 14, you actually see that variability and sensitivity and how the slope changes, especially when you shift it. So, I think there's...even with the little bit of data we have

insight into, I see variants changes, slope changes.

DR. MOORE: But if you go to the next slide...you have that? Oh, no, we don't have. You may have to make the plots with mallards and...and bobwhite quail, and actually, slopes don't look that different, but, I mean, there are only a limited number of slopes that have been reported in the literature. For carbofuran for birds, they're all steep, and is there variation in slope? Absolutely. Is it systematic according to sensitivity of the birds? I'm not sure of that. I'd have to look into the data.

But there is...they're all steep. They're all fairly close together. So, that's why we made the assumption of...of equal slopes for our three hypothetical species.

And I would further note that this is the exact same approach that's taken in TIM Version 1 and 2.

DR. PORTIER: I don't doubt that. The other thing is if you shift those lines, you shift it in 3.8x over, again, you have no data to show that the slopes never vary, the slope of that line doesn't shift as well.

DR. MOORE: You're right.

DR. PORTIER: Which means that you could

be sliding over, but some of the lower bound ones would still be...so, anyway, the point made.

DR. MOORE: Yeah, I...I can comment on that one. For a bobwhite quail which is one with...where we have more treatments, we did do a...a pointed curve for the aqueous bolus treatment and the food matrix bolus treatment, and once you do that, you can calculate, say, an LC5, an LC50, and an LC95. It varies from 3.84 at the low end to 3.94 at the high end.

DR. PORTIER: Oh, okay, that helps.

DR. HEERINGA: Okay, I'm going to have to draw the question and answer period on this particular presentation to a close simply because we have three more presentations to finish, I think, today. I want to thank Dr. Solomon and Dr. Moore and the panelists.

I think, panelists, if there are critical items, and I know several of you are raising your hands, I think that we can get them answered at the break. Obviously, if you have a conversation, you need to report it back here publicly in terms of any findings that would influence your recommendation.

So, at this point in time, we're going to make an exception in the agenda. We're going...I'm

going to ask Mr. Ray Young...and this has been approved by the relevant parties...who is a farmer and crop consultant with Young & Young Consultants, I believe with his son. He has a short public presentation, and then we will return to the sequence of presentations by FMC.

Mr. Young?

MR. YOUNG: My name is Ray Young, and I'd like to thank Dr. Matten for giving me the opportunity to speak to this distinguished panel here today. I'm an independent crop consultant and a farmer in northeast Louisiana.

By independent, I mean that we deal with individual growers and that our business is in no way concerning with crop sales.

I grew up in the '30s with my family, farming cotton. We plowed the mules, chopped the cotton, and picked the cotton. In 1931, my two older brothers went to the Navy, and I was left to farm by myself at a pretty young age, but during that time, I like to say that we used nicotine sulfate to control aphids, and we used Paris green to control leaf worms. Pretty bad combination when you shook it out with a cloth flour sack behind and you're through it.

In 1939, I began scouting cotton. That was

the very beginning of agricultural consulting as a profession as...as we know it today. I received a bachelor's degree from Louisiana Tech in agriculture in 1950. I served four years in the Navy as a carrier pilot. I returned to civilian life, enrolled in LSU, and received a master's degree in entomology in 1957.

I'm still actively involved in farming and consulting with my son, Jesse. We give advice to growers on every phase of crop production from seed selection to harvest preparation. For the purpose of my discussion today, I'll limit my remarks to our dealing with insect control.

In our business, we're constantly on guard to prevent insect resistance. This is a problem that we've encountered through the years, and we...we deal with this problem by alternating chemistry.

My first experience with insect resistance was in 1955, cotton boll weevil that was living through the chlorinated hydrocarbons. That was not a pretty scene.

Since that time, we have seen resistance develop in several classes of chemistry and several insects, including the tobacco bollworm, the tobacco bloodworm, tarnished plant bugs, and the cotton aphids.

There have been problems with aphids

sporadically throughout the cotton belt for many, many years. It's sporadic occurrences, but you never know when they'll show. Aphids develop resistance very rapidly because of the frequency of generations. If you look at figure 1, you'll...you'll see an overlapping of generations.

Aphids develop through a process known as parthenogenesis. That means that they give live birth to fertilized females. Generations occur in 7 or less days, depending upon temperatures.

So, you can see that these insects can very quickly wrap up a whole plant, and when they do, they damage that plant very quickly. These aphids excrete a liquid called honeydew. That honeydew goes onto the green leaves, setting on a fungus forms and grows and interferes with photosynthesis. When that honeydew gets on the lint as the lint begins to open, as the bolls open, it causes a set of mold, and this destroys...destroys quality and, hence, the price.

Over the years, many products have...aphids have gotten resistant to many of the classes of...of insecticides, the organochlorines, organophosphates, synthetic pyrethroids, and some carbamates. Furidan is a product that is effective. It has been effective through the years. We've trusted it, and we return to

it for our worst case aphids.

For the past several years, we've had a new type of chemistry called the neonicotinoids that have worked quite well until the last couple of years, but we are beginning to see a weakness, because they've been applied to a good portion of the crop producing area. As we lose these products, we'll lose control.

If you look at figures 5 and 6, look at figure 5 first. That's in 205...2005. You'll see that all products at 7 days gave excellent control of aphids, 70, 84, 80 percent control. And that's at a half rate for Intruder and Synthra.

Now, look at figure 6, and you'll see that in 2006, these products, at full label rates, were less than adequate control. You will note, however, that Furidan stands out among the bunch as still being very effective.

We had one failure a couple of years ago, and in that failure, furidan was granted on section 18, and it cleaned the aphids up very nicely. If we lose furidan, we lose a very important resistance management tool.

Cotton is a vital part of the production of agricultural products across the southern United States. Furidan is a vital product for managing

insects in cotton. We don't need to lose this important resistance management tool.

I feel very strongly about this testimony because of my experience with insect resistance through the years and my experience growing cotton for the past 67 years.

I thank you for your attention, and I appreciate your working me into your busy schedule, Dr. Matten. I would be happy to attempt to answer any questions that you might have.

DR. HEERINGA: Thank you, Mr. Young. Any questions for Mr. Young?

(No response.)

DR. HEERINGA: Thank you for that presentation.

MR. YOUNG: Thank you very much.

DR. HEERINGA: An example of conciseness.

I've been informed of the Designated Federal...by the Designated Federal Official we need to have a short administrative meeting of the panel in our breakout room, so I'm going to call a break, and when we return, we'll resume with the...the next of the public presentations. Panel members, if you could just join us here.

(WHEREUPON, a brief recess was taken.)

DR. HEERINGA: As soon as we have a Designated Federal Official, we'll get underway. Okay, we're ready. Okay, we're...we're going to be ready to resume, and before we begin with the next presentation, the Designated Federal Official, Sharlene Matten, has a few clarifying comments.

DR. MATTEN: Yes, this is Sharlene Matten. I...I just wanted to clarify a remark or a set of remarks that were made this morning about the Federal Advisory Committee Act and duplication of efforts.

EPA has a longstanding policy of trying not to do the exact same charge between two different Federal Advisory Committees, one being the Human Studies Review Board and the Scientific Advisory Panel. After much discussion, a new light has been shed that there...there may be some nuances in understanding of different scientific questions that weren't addressed specifically by the Human Studies Review Board that could be available for some sort of discussion of those very same studies that had a specific set of charge questions related to them.

And so, the panel may have some discussion on these studies related to those specific set of issues

that weren't previously addressed that wouldn't overlap two dif...overlap charges between two different federal advisory committees. And, hopefully, that makes some sense.

I'm a little overwhelmed by the number of attorneys that have been advising over the last several hours, but I...I hope that clarifies things just a little bit. It doesn't completely clarify it for me, but...so, I think you can continue.

DR. HEERINGA: I think we will continue. That's...that's probably the best...best step to take at this point. And, again, just to reiterate, our focus here is on full scientific exploration and development of the issues at hand, and we're going to do that, and we'll accommodate processes and legalities and everything else as we go, and thank you very much.

And I apologize to the audience for the abrupt recess there, but we're ready to move on now, and we are, I think, to the next of the presentations, and this is the worker risk presentation.

DR. LAMB: That's correct.

DR. HEERINGA: And Dr. James Lam of the Weinberg Group, is going to be the leader.

DR. LAMB: That's me. I'm Jim Lam. I'm with the Weinberg Group, and I was asked by FMC to

review the toxicology data, and in this presentation, I'll talk for a very surprisingly short time about the worker data on the toxicology relative to the worker risk assessment, and then Dr. Jeffrey Driver will talk about the exposure, occupational exposure assessment.

In the first slide is simply an outline of the major issues that I will cover. The outline may give you a sense this is longer than it really is. I really think that this is going to be 15 minutes' worth of touching on what to ask as the most important issue.

Ultimately, worker risk assessment is evaluated by comparing the point of departure to potential field exposures, and they look for margins of exposure and...I hope everybody can hear me...the margins of exposure generally need to be 100 or more. The...the bottom line comes to that EPA's calculations in the Notice of Intent to Cancel and the interim red have scenarios for the selection of point of departure and exposure assessment that gets you to less than 1 to about 50, so they are considered by EPA to be unacceptable.

FMC's worker risk assessment actually demonstrates that the occupational exposures are acceptable with margins of exposures between 110 and 3400, and I will explain that as we go through.

But there are really two major issues. One is the issue I will talk about, and the other is the issue that Dr. Driver will talk about. First, EPA's assessment, I think as you already know, doesn't use the guideline dermal toxicology study. Instead, they have taken an oral toxicology study.

Both look at brain acetylcholinesterase, and then they take the oral study and adjust using the dermal absorption factor from the Shaw study.

My position is that you should be relying on the der...21-day dermal study. No absorption factor is necessary in this approach.

Dr. Driver will talk about that EPA's position is relying more on older exposure assessment tools, and he'll be talking about the new exposure assessment methodology that is...that is being used by EPA, but it's not being used yet by EPA in this assessment.

There is...very quickly, because I know you've heard all this stuff before...the margin of exposure is, basically, take the point of departure for the critical adverse effect and divide it by exposure, and we're looking for margins of exposure greater than 100 for acceptable uses. The EPA approach and the FMC approach basically end up with numbers that differ by

two orders of magnitude so that if you took the same exposure number which, in this example, is 0.016 mg/kg/day, that the two different points of departure, you would end up with very different margins of exposure.

Bottom line as a toxicologist is that the point of departure, the selection of the point of departure, the study that you're using to select that point of departure is critical. Typically, EPA will use dermal toxicology studies for pesticide mixers, loaders, and applicators.

Just to make this really clear, the interest here is adults, and it is dermal exposure. It is usually done that they use a 21 or 28-day rat or rabbit dermal toxicology study, and there are testing guidelines that exist that describe the testing methods and the endpoints that need to be evaluated.

These are examples of studies, carbamates and organophosphates, where that approach has been taken. The...and we will get at..this is simply to give you a sense that this is not a...an issue of first impression.

EPA, though, in this particular case, has used an oral point of departure of 0.02 mg/kg. It's based on adult rat acetylcholinesterase inhibition, and

it has to be, since it's an oral study and our concern is primarily dermal exposure, it has to be adjusted for dermal penetration.

The study that they have and have relied upon for that is the Shaw study, and I think Dr. Shaw was up here earlier today. They, like us, are looking for margins of exposure that are actually greater than or equal to 100, but typically, they only take this approach when they lack valid dermal toxicology studies.

In...in this case, they basically classified a valid study as unacceptable and leads them back to this position. They've rejected the use of the dermal study, and I believe that is, in fact, an error.

The studies are that...that the 21-day rat dermal study was submitted. FMC has used this. Now, this study was created in response to...there was already a rabbit dermal study submitted to EPA. It's my understanding that EPA was not satisfied with the findings, that the...they didn't believe the no observed adverse effect level could be that high, and so that they asked for another study.

It's also my understanding that at that point in time, they did not ask for pharmacokinetic data or time to effect or time to peak response. They asked

for a dermal toxicology study.

There are also human dermal studies. I think you've already heard a little bit about the issues in these. I really don't see that the human studies play much of a role in this case in any event.

But the review of the 21-day dermal study does. In the EPA data evaluation record, basically, they rejected the study specifically because the information did not include time of onset, time of peak, and time until recovery. That sort of pharmacokinetic or pharmacodynamic information is not in the guidelines for the dermal toxicology study, it wasn't requested by EPA, and as far as I know, it hasn't been used in a worker risk assessment.

I have an example where it was asked for, for example, on carbaryl. It's not even clear it was used even after they got those data, but I think, actually, more important than...than the administrative aspects of this is whether or not the data are really needed.

The most appropriate study is the one done by the same route of exposure. The toxicology study to evaluate dermal risk, the best one is the dermal toxicology study. They have a good study in their file. It's the same as has been used or very similar to those used for other carbamates and other

organophosphates.

We need to talk a little bit about some of the specifics, because I'm afraid there may have been some confusion about the study this morning. It was a 6-hour exposure. Now, my understanding of what I heard this morning from EPA was they want now time to effect. At the end of the 6 hours, they would want sequential evaluations. That's what I heard.

This study was done with a protocol specified that no sacrifice should...should be later than 6 hours after the exposure ending. I have to admit that we went back and looked at the time to collection. The average was 6 minutes. So, they clean...they dosed for 6 continuous hours.

Now, this is a product with a pretty fast half-life. They dosed for 6 hours, and right at the end of that, they cleaned the site, and within an average of 6 minutes, 7 for females, 6.1 exactly for males, they...the animals were killed, the samples were collected.

The...the...there were 2 animals that were 12 minutes after sacrifice, 1 was 11. All the rest were 10 minutes or less.

There was not time...my opinion is that it's...I have no data in the rat with carbofuran, but

if what they wanted was a 6-hour exposure and then we start looking at response, it...it's nearly implausible to me that the response is going to go up after we've cleaned the application site. And so, the rapid sacrifice was considered important, and that's the way the study was done.

Out of that study, brain acetylcholinesterase was evaluated. The no observed adverse effect level in that study was 50 mg/kg/day. There was significant suppression at 250, the next highest dose level. There are a couple of dose levels below this which confirm the lack of inhibition of brain or RBC cholinesterase.

In our opinion, and we hope the SAP will consider this very seriously, that this study should be accepted and used in the risk assessment. This is the best model, the best science that's available at this point in time.

Now, the other points, in addition to the 6-hour exposure giving time for the peak to occur and then, according to typical guidelines, and sacrifice pretty quickly, the...the only value that I would say the human study might provide...and I'm really not going to push this very hard; I don't think it's that important...is whether or not...is basically the human study does show some...that the peak did come on. It

came on slowly.

There's also a carbaryl absorption disposition metabolism and excretion study. It's a different carbamate. It's at relatively high dose levels, but it does show that dermal penetration continued in that study pretty much throughout the study.

And there's not a whole lot else I can offer you in the science.

The RBC data they listed as part of the reason this study was rejected as well. The real focus was the lack of pharmacokinetic data, but I wanted to address the point of variability in the RBC data in this study.

As you can see from these coefficients of variation...and you...I will say, too, that the FMC reports that you've seen to date typically show standard deviations. EPA's show standard errors. So, with group sizes that are generally 10, our bars are going to be three times bigger than everybody...than the EPA ones, and that really is more the reason you see this variation. These were not group sizes of 2 or 3 animals. I just want to be really clear on that.

But the coefficients of variation in this study are not remarkable. They're not huge.

The weaknesses of the current approach proposed by EPA is it's ignoring a valid study, a valid dermal tox study. It calls for unnecessary manipulation of the oral toxicology data. And they're approach, in fact, does not address that very pharmacokinetic information that they're asking that be provided through the dermal study.

Also, the dermal study was not designed for this purpose, so to be fair, it was done 20 years ago, designed for a different purpose, and those data are limited.

You don't have the raw data which, in our case, of course, any FMC study goes to the Agency with all the underlying raw data in considerable detail.

The approach that was taken was sampling times of 2 hours and 24 hours and...and afterwards as well meant that the exposure continued all the way out to 24 hours. Acetone was used as a vehicle. That has a high likelihood that it would enhance absorption of the material because of the breakdown of the skin.

They didn't clean the application site, as I mentioned, and also, they did not, in that study, because it was not designed for this purpose, they didn't measure acetylcholinesterase or its inhibition.

Their approach, the EPA approach, frankly,

does not improve the risk assessment. They don't model the workday the way they developed it. The oral study and the dermal penetration data together do not provide information on dermal pharmacokinetics

The be...the preferred method is, frankly, the use of the dermal toxicology study that's been provided. These were 21 consecutive days of treatment. I think you heard this morning it was 5 days a week, and that really isn't correct, but I completely agree with Ginger Moser that it...it doesn't matter. The 1st day is probably going to be pretty much the same as the 21st. So, I'm...I don't think it makes any difference whether it was 5 or 7. It was 7, and the sacrifice was within minutes of the end of the treatment.

And bottom line is you should be using the 21-day dermal study. The point of departure should be the BMDL of 50, that they should...EPA should not be rejecting the study on the basis of this pharmacokinetic data requirement.

And with that, I'm going to pass the microphone to Dr. Driver to move on to worker exposure and then you can ask...it's up to you, Dr. Heeringa.

DR. HEERINGA: That's what I was going to suggest, and I want to thank you for conciseness and the base of your presentation.

DR. LAMB: No problem. Thank you.

DR. HEERINGA: Dr. Driver?

DR. DRIVER: Thank you very much. Thank you, panel, for your continued endurance. I'd like to briefly turn your attention to the carbaryl worker exposure risk analysis.

SPEAKER: Carbofuran.

DR. DRIVER: Carbofuran. Sorry. Pardon me. The...the purpose of the impact of...or the purpose of my presentation is to demonstrate the impact of using what we propose is the appropriate toxicology benchmarks, route-specific benchmarks, as well as the best available exposure monitoring data.

My outline includes a brief overview, contrasting EPA's assessment with what we're proposing. I'd then like to, by way of background, just discuss the routes of exposure and the more simplistic exposure assessment algorithm that's used for tier 1 deterministic calculations in contrast to relevant stochastic modeling you saw earlier, so I'll bring you back to elementary school math, the exposure reduction via closed systems that are...that are used by carbofuran, and I comment on those engineering controls, and also the exposure monitoring data that are available to inform the exposure analysis, and then

my results and conclusions.

So, with respect to an overview, as we heard, EPA's assessment did address both dermal and inhalation routes for workers, appropriately. In...in both cases, the toxicology benchmark was based on oral routes, BMDL10, necessitating, in the...in the case of the dermal route, an absorption factor. As has been pointed out, this inherently assumes, then, that the dermal exposure results in...in essentially an instantaneous bolus of pure dose, if you will, via the dermal route as it's compared, then, to an oral benchmark dose.

The exposure estimates were, appropriately for a tier 1 assessment, based on standardized scenarios in the Pesticide Handler's Exposure Database and associated assumptions. The resulting MOEs are listed here at the bottom of the slide. As..as has been mentioned, they range from approximately 1 to 50.

On the right-hand side, we see FMC's refined assessment. In this case, as Jim had mentioned, we're looking at the dermal toxicology studies, the basis for the dermal benchmark.

In the case of the inhalation route, as is commonly done in the absence of an inhalation study for this compound, carbofuran, it's based on an oral point

of departure. In this case, a value was selected representing that derived by EPA for children which would be protective for adults as well.

In this case, no dermal absorption factor would be necessary, of course. We're using applied dose dermal NOEL to compare to external dermal exposure on the workers as you estimate it.

The exposure estimates, then, as the next bullet indicates are based on data specifically selected to represent exposures for workers involved in using engineering controls that are used for carbofuran in liquid applications.

In addition, we made some respiration rate adjustments that I'll talk about for activity level specific tasks that workers are undertaking. The contrasting MOEs are listed there, ranging from 110 to 3400.

This difference in the MOEs, in part, obviously, is due to the difference in the toxicology benchmark associated with the dermal route. These are total MOEs, by the way, across both the inhalation and dermal routes. So, the difference, obviously, is largely, in part, related to the difference in the tox benchmark but also in...in terms of the exposure estimates, as I will explain.

By way of background, the primary route of exposure in...in most worker situations is the dermal route, followed by inhalation. Engineering controls can mitigate and, in both cases, reduce exposure significantly. Carbofuran has very low vapor pressure, so dermal route is...is typically the largest exposure route of interest.

The exposure algorithm, very simply stated here, is a function of the amount handled, as far as what we refer to as the unit exposure metric divided by body weight. The amount handled is typically expressed as pounds of active ingredient handled. The amount handled often is assumed to be a maximum application rate, maximum acreage treated, so we're biasing that towards an upper end of the distribution. We...we intend to do that.

The unit exposure is typically expressed as mg of exposure per lb of AI handled.

I'd like to...to briefly inform you about closed system technologies. The worker protection standard developed by EPA has defined the...these technologies, properly functioning systems that enclose the pesticide, of course, and prevent it from contacting handlers or other persons, and studies have been done and summarized that demonstrate, in this

case, the mean reduction in exposure relative to conventional open mixing and loading, 96.8 percent. This was from five studies that the California's EPA's Department of Pesticide Regulations had reviewed.

The systems specifically used with carbofuran include the micromatic drum valve system. I have some examples here, and this would be fit to a 110-gallon mini bulk container or a 15-gallon returnable container. There's also a smaller container, 2.5 gallon, that utilizes a secure LG system.

Just for purposes of...of reminding us, this is a picture of an open mixing and loading system, obviously. This is not what's used with carbaryl...carbofuran. Sorry. I'll get it right eventually.

This diagram actually shows the micromatic drum valve system, and it basically creates a dr...what we refer to as a dry lock system that minimizes the leakage. Technical specifications for this type of system would be approximately 1 ml residue leaking or less. Obviously, that's going to significantly reduce operator exposure, and there are a variety of other benefits that are mentioned here.

The schematic in the lower right-hand column, if you can actually see that, just shows in black there

where these valves would be located at the top of the container. We actually have a container here to your right. Okay, I'll keep going.

So, what my friend, Dan O'Ryan, is now picking up is the larger...this actually is the 25-gallon container...or is that 15? 15, sorry, 15 gallon container. The valve system is on the top, the stainless steel valve system, so that...that's obviously dry locks. The hose, then, would be connected to the top of that valve system, creating a sealed container for...these...these containers actually can be returned and...and re-used after appropriate rinsing.

There's a smaller container here at the bottom here, too, that you can look at at your leisure.

Here's a picture of the secure NG closed system for the 2.5-gallon. It's basically a...a valve, a top, you see, that screws on the container, again, creating a secure system. There's some pictures on the graph here and some more that you can read about if you're interested.

In addition to closed mixing and loading systems, open cabs...or closed...I'm sorry...closed cab systems are another engineering control that's used with carbofuran. This is an example of the open cab,

in contrast, that a tractor operator obviously...and this happens to be air blast in an apple orchard. In contrast, here's a picture of an enclosed cab ground boom application rig.

As indicated in EPA's guidance, enclosed cabs can result in up to 98 percent reduction in both dermal and inhalation exposure. So, in the case of carbofuran, we have these engineering controls that are being used.

And so, it's important to use exposure monitoring data, then, that were developed with workers using these controls. So, our proposal is to...to consider those more relevant data. They include data submitted to EPA by the Agricultural Handlers' Exposure Task Force. There also are some data relevant within the Pesticide Handlers' Exposure Database that can be subset and used in addition to...to the AHTTF data.

And, finally, I'd also mention that the inhalation exposure data can be and should be adjusted...and this has been agreed upon through some harmonized discussions with regulatory agencies...task and activity level specific respiration rates. So, persons, for example, piloting an aircraft or driving a tractor would be breathing at a lower rate than someone with a lot of physical exertion.

This, just quickly, gives you a map, if you will, of the available exposure monitoring data that we would propose for use. There are two studies from the task force. They've been submitted to EPA, as indicated by their...what are referred to as NRID numbers. They provide a total of 22 monitoring units. A monitoring unit can be thought of as a set of measurements for each...for a unique worker.

In addition, two studies have been provided for closed cockpit aerial applicator exposures of liquids.

There are also 9 monitoring units completed thus far for a closed cab ground boom application of liquids. However, they haven't been submitted.

There are data within the Pesticide Handlers' Exposure Database that can be used, adjusted for an appropriate respiration rate.

The next slide just simply provides comparisons of the central tendency values, the unit exposure values expressed, in this case, as g of exposure per pound AI. So, on the left-hand column, you have these three scenarios I've been mentioning, closed system mixing and loading of liquids, fixed wing aerial aircraft applicator exposures, and then the ground boom tractor drivers in enclosed cabs.

So, we have both the inhalation and dermal routes and their respective unit exposures for either the PHED data or a refined estimate that has been adjusted based on respiration rate in the case of the inhalation route, followed in the final column with the AHTTF unit exposure values. I have bolded those values that we're proposing for selection.

I've indicated the values shown here are geometric means. The values listed here for PHED depend on the best fit analysis within the database. Typically, it's either a log normal or geometric mean, a normal arithmetic mean, or an other categorization in which a median value would be used.

The role of...of task force data and other studies, too, that have been collected are going forward and, in the recent past, have been, in fact, the subject of...as well as the existing PHED data have been a...a subject of discussion at a recent, January, 2007, science advisory panel. Some of the panel members here were involved in that. It was an excellent discussion. We...we all...there was concurrence about the need to develop new data and a lot of great discussion about how those data should be collected, study design, sample size, and a variety of other statistical considerations.

In general, agreement was that additional data would significantly improve the assessments. In fact, the primary purpose of the task force, as you can imagine, is to address some of the deficiencies in the existing data.

For example, the upper...upper left schematic of the gingerbread man represents...the Os and Xs represent locations of patches, patch dosimeters, small square dosimeters that would be used at...at located throughout...across the various body part areas of an individual. This is sort of the historical method for collecting dermal exposure monitoring data both for outer and inner, outside being outside the clothing and then underneath the clothing.

The lower right hand column represents the preferred method which is a whole-body dosimeter. This is an in...inner dosimeter that a person would wear underneath their work clothing.

There are a number of advantages to the der...that use of the dermal passive dosimeter, in part, for example, as this bullet indicates, in looking at some of the limitations of existing data, including the patch type monitoring, for example, as the first bullet indicates, you may often have an inadequate number of measurements for one or more body areas, in

other words, missing patches, so that one would have to extrapolate from another body part area to...to estimate a value.

There were limitations, skipping down a few bullets, of...of censored data, many values being below the detection limit, particularly with inner dosimeters, and there are some other limitations mentioned here that you could read at your leisure.

So, the role of...of collecting data such as those represented by AHTTF are probably obvious, but let me just highlight a few things here for you. The data, as I've mentioned, exist. The data, AHTTF data, do exist for carbofuran representative of closed mixing and loading systems and aerial application. There are examples recently where EPA has also selected those appropriate studies, aldicarb, carbaryl, and I think they could be used here. Those studies were all conducted under good laboratory practices. So many of the historical data sets were not.

The limits of quantitation, as you can imagine, analytical sensitivities were lower, so we have a less...a lower proportion of censored data, the use of full-body dosimeters, and, very importantly, joint regulatory committees, EPA, PMRA, California EPA have been involved, staff have been involved in the

design of these studies.

Another important aspect is that, from an allometric standpoint, body surface areas are proportionate to the subjects' body weights. I had mentioned respiration rates that are task specific so that non-physiological rates aren't used for low activity tasks.

And the data represent full workdays in terms of the monitoring period that they represent.

So, these studies can be used preferentially for occupational assessments for liquid pesticides such as carbofuran.

As Jim had mentioned, the toxicology endpoint selection is critical. Preferentially, if route-specific data are available that are considered valid, they...they would be used. The dermal assessment can be based, we think in this case, on the dermal 21-day study, and as I had mentioned, the oral point of departure can be used and has been routinely for the inhalation risk assessment.

This just provides you with a sampling of total margins of exposure across both routes for three scenarios. The unit exposures used, the acres treated assumed, and the resulting MOEs, corn...these are for corn application scenarios which happens to be the

worst case scenario for carbofuran. The...the details of our assessment are provided in written materials submitted to the panel, to EPA.

And, finally, in conclusion, we would propose consideration of the route-specific toxicology data, the refined exposure monitoring data that would be available, and using those data demonstrates acceptable risks in the case of carbofuran occupational scenarios.

Thank you.

DR. HEERINGA: Thank you, Dr. Lamb and Dr. Driver.

DR. DRIVER: I do have one last slide. I'm sorry.

DR. HEERINGA: Sure.

DR. DRIVER: These...this is just prompts, some questions for the panel to consider which...which, I think, are obvious, but, you know, use of the 21-day dermal study in contrast to an oral study and the uncertainties that that may introduce, and, secondly, use of the exposure monitoring data.

Thank you.

DR. HEERINGA: Thank you very much. Questions for Dr. Lamb or Dr. Driver? Dr. Hattis, okay.

DR. HATTIS: Yes, I have two questions.

You've got geometric means here. What are the associated geometric standard deviations?

DR. DRIVER: I don't...I could provide that to you. I don't have that with me.

DR. HATTIS: It's not in your written materials or anything?

DR. DRIVER: I don't think it is, but I can provide them to you.

DR. HATTIS: All right. And then, second, do you have any surveys of actually uses of carbofuran to see how...how often these wonderful new procedures are actually employed?

DR. LAMB: Don, do you?

DR. HEERINGA: Be sure to introduce you, I think, Dr. Carlson.

DR. CARLSON: Yes, my name is Dr. Donald Carlson. I'm with FMC Corporation.

Actual surveys, we do not have actual surveys. The equipment itself, as it's been demonstrated, is the only equipment that is available. It is sold only in these types of containers. In the 2.5 size, all of it is in 2.5 with the Sotera link G with the exception of California. California requires puncture box systems, and in that case, it goes into a puncture box system.

We do have, obviously, data which is collected by the 6A2 reporting in order to go and look at whether there are affected work incidents of any type, and that is available if you would like to look at it.

DR. HEERINGA: Dr. Brimijoin and then Dr. Edler.

DR. BRIMIJOIN: Just a quick one. So, your assessment of the...which...which includes lines on the 21-day rate dermal test study indicates that, in some cases, there are large NOEs and, in other cases, sort of in the...at the border of acceptable, on...on the good side but close.

So, what happens to this effect if EPA were to accept the 21-day dermal toxicology study, but given that it has already determined that, in general, the RBC is more sensitive than the brain and has already determined that your RBC data from that study are in...are not acceptable, what...what will that do to your NOEs?

DR. LAMB: First, let me make it clear that...and I do actually make it clear in the discussion of the oral study. RBC in adults, EPA even says, is not more sensitive, despite the chart they keep throwing up. That...there's a data point that's

in error there, and they have concluded, and I think it's even in the issue paper that you've received, that RBC is not more sensitive than brain.

I'll also, in the next presentation...but I can't miss the opportunity...will mention that, obviously, it's very valuable for certain studies, but EPA and...and I agree...EPA has said and I agree, it's a surrogate measure. The adverse effect is brain acetylcholinesterase activity, and the inhibition of that activity is the adverse effect.

DR. HEERINGA: Dr. Lamb, you should touch off that microphone right next to you.

DR. LAMB: I'm sorry.

DR. HEERINGA: Other questions? Dr. Edler and then Dr. Lu.

DR. EDLER: Lutz Edler, German Cancer Center. I have just a question, Dr. Lamb, about the NOE calculation at 50 mg/kg. I think we have very nice dose response data in this case, so I was wondering if somebody has actually calculated a benchmark dose with these data.

DR. LAMB: I don't know that anyone has done...we have not done a benchmark dose calculation. The data...the data, though, show clear inhibition at the five-fold higher dose level of 250 and not

inhibition at the 50 for brain acetylcholinesterase inhibition.

DR. DRIVER: And just a correction. In our written report, we did provide a benchmark dose calculation for the dermal route.

DR. LAMB: I don't think so.

DR. DRIVER: We didn't?

DR. LAMB: No.

DR. DRIVER: Okay. Sorry, okay, I...I stand corrected.

DR. LAMB: I don't think it's there.

DR. DRIVER: 4.7.

DR. LAMB: He's just causing trouble. I don't think it's there.

DR. DRIVER: That must have been for carbaryl. I thought we did.

DR. LAMB: No, as far as I know, it doesn't...it has not been calculated. So, I thought the NOAEL worked pretty clearly, and, you know...

DR. HEERINGA: Dr. Lu and then Dr. Morton.

DR. LU: I think you...your points are well taken, and you have addressed most of the concern that EPA raised in their presentation yesterday, but, apparently, you omitted one point which I think is

critical. It's the performance of the contractor lab on the samples. Can you comment on that?

Because what I'm getting by reading the...the documentation and EPA's presentation is that there are some issues associated with the analytical protocol that actually introduce this continuing reactivation of the enzyme activity. So, the resulting data look like there's no inhibition at all, but the question is, is that truly inhibition? The moment you collect the sample from the...the rat, and then, is that reactivated continuously?

And if that's the case, then, my opinion, without how good the study was designed, the data is not...cannot be used, and, you know, that's probably the case. Or you can comment on this.

DR. LAMB: Thank you. The...it's really important we separate these out. One is that the issue is exclusively RBC cholinesterase inhibition or RBC cholinesterase activity assays at a particular laboratory. Brain acetylcholinesterase is really the critical adverse effect that's being moni...modeled in this 21-day dermal study. It's the correct point of departure.

There are no questions about or issues that I've heard about the brain acetylcholinesterase

activity. So, it's almost like...EPA has talked a lot about the RBC issue, and...and my view is we should basically...we can remove that from consideration in this case.

And in this particular study, the brain acetylcholinesterase activity responds very quickly. It responds...it recovers quickly. It is certainly a...an example of an effect on the central nervous system. It, in fact...and I'll go into this in my next talk as well...the brain appears to be, in adults, the first endpoint that responds even in the EPA studies.

For example, the McDaniel study, I believe, at 0.1 mg/kg/day, the brain responds in the EPA...that's an EPA lab, different assay. It's not until 0.3 mg/kg that RBC and motor activity start to respond.

So, in the adult, the...if anything, the brain appears to be not only the most relevant but also the most sensitive endpoint and should be used...and should be completely valid in...in this particular 21-day dermal study.

I hope that answers your question.

DR. LU: This is Alex Lu again. I guess my...my...let me put my question this way. Say you are able to split the...the blood sample. Doesn't matter

if it's brain tissue or red blood cells. And you have your contract lab analyze for cholinesterase enzyme activity, and then you send it to EPA. Would you expect this...the number from this blood sample will come in agreement?

It look like that it won't, because, I mean, there are many problems that I can...I can, you know, envision associated with the protocol that your contract lab used, and one of the most critical points is that the sample was collected and sit on the ice for an hour. So, if you think that the reactivation of the enzyme activity inhibit by a carbamate or, in this case, carbofuran was so dramatic, so rapid, then that 1-hour window of time will wipe out all information resulting from dermal exposures.

Do you agree?

DR. HEERINGA: I was waiting for the question mark, Dr. Lu.

DR. LAMB: I was, too. No, I don't agree, because I don't believe you're really looking at the correct critical effect. I think it really needs to be the brain acetylcholinesterase inhibition where you don't have the same issues.

DR. HEERINGA: Questions of clarification? I'm going to go now to Dr. Bunge and

then to Dr. Chambers.

DR. BUNGE: On...

SPEAKER: Your mike went out.

DR. BUNGE: Thank you. I'm a specialist in dermal absorption but not cholinesterase inhibition, so I may be asking as naive question, but one of the issue...the analysis method, the modified Elman's reagent method, was used for both the red blood cell and the brain tissue.

Is the problem that EPA has discussed potentially occurring with the red blood cell, would it not occur in the analysis of the brain tissue? In other words, is...what's different about the two tissues?

DR. LAMB: Right, right. I think that the most significant issue with the red blood cell was probably the dilution or rinsing of the red blood cells which was not done with the brain. So, I do think that the assays...there's a reason one is responding and...and appears reliable and the reason the other does not.

DR. HEERINGA: Thank you.

DR. CHAMBERS: Jan Chambers. The last chart you had there with the NOEs that you calculated, just clarify for me, did you use the AHTTF values for

that then?

DR. LAMB: Yes, right.

DR. CHAMBERS: All right.

DR. HEERINGA: Dr. Bunge?

DR. BUNGE: Annette Bunge again. Could I have some clarification on how you establish the no effect, no observable adverse effect level at 50? When I look at the study report, at least in terms of the means, and I did go through a statistical analysis, if I look at the mean values of the cholinesterase levels in the brain, I see they're reduced at lower doses than the 50. Can you explain the decision to choose 50?

DR. LAMB: The...the selection of 50 was the study authors' selection, but I really think it's based on a combination of statistical significance and the degree of cholinesterase inhibition. It...it's not articulated in the report. I think it's...if it's not 50, it's real close.

DR. BUNGE: The report doesn't discuss the NOAEL at all, and...and we have, at least as near as I can tell...I think I've gone through all of my piles of papers and electronic files...their report describe how you took the data to determine the no effect level. Maybe I'm mistaken. If we have a document about that or if we can get one, it would be

helpful.

DR. LAMB: Okay, what we can do is look at that and provide you something probably later today or in the morning.

DR. HEERINGA: We'd like to have a reference or if it requires a separate justification, to provide it, that would be very helpful.

DR. LAMB: Sure.

DR. BUNGE: Actually, I had a few more, but I'll ask one more and then let other people have a chance. Now I've forgotten what I was going to ask. Oh, yes, back to the issue of the...the timing and maybe we should ask the EPA folks again, but I think the issue wasn't a pharmacokinetic issue. It was the issue of the sample handling. So, the samples were collected more or less immediately, but then, they could be held on ice for up to an hour, according to the protocol.

And so, the question is, what about that one hour on ice? What effect might that have had on the measurement?

DR. LAMB: I had the impression from what EPA has written and said that it...it was both in that the problem, one, it...the understanding that EPA had was that it sounded like they didn't think the

analysis was...even the sample collection was likely to happen for an hour after the...after the cleaning of the site. That's, as I mentioned in my talk, that's not correct.

But it...it really sounded to me like they were looking for data in a time course, much as you have the data in the time course for the oral study where they looked over a period of time and, as they described it, from the time the dosing ends, they would then look for whether the peak...when the peak comes, what the time is to the peak, whether that changes.

So, it's my understanding, from what they've written and said, that's what they want, but you might be right, that we maybe need to ask them, because it's not fair for me to say much about that.

DR. BUNGE: If I can follow up, then let's assume that you...you did have the samples collected almost immediately following the end of exposure, but they could be held as long as an hour on ice, according to the protocol. What effect would that have on the data, the results?

DR. LAMB: Well, it's a...it's a fair question that I don't have the answer to. It's...and I...just as I have...just as I asked for how long did we really have the animals there for an hour, the

answer was no, it was 6 minutes. I don't have the data as to when they analyzed the samples compared to that point in time, and I don't even know if they exist, but we could check and see if they do.

That's the best I can do on that one, and I really don't know that that's going to answer your question, because that sort of time course was not done. That's sort of...

DR. HEERINGA: Yes, Dr. Stinchcomb?

DR. STINCHCOMB: Audra Stinchcomb, University of Kentucky. Could you describe the application procedure in the dermal tox studies and how it's better than or different from the acetone deposition study?

DR. LAMB: I really think one of the biggest differences in...is that the acetone deposition study created a slurry with acetone as the vehicle, and it...it's my understanding from people who worked in this area that that is likely to degrade skin and facilitate absorption beyond what you'd normally expect, whereas the dermal toxicology study is not using an acetone slurry. It's using the product either as a formulation or diluted in water and then applied to the skin.

DR. STINCHCOMB: It was applied in both

ways or...

DR. LAMB: I'm told it was...no, I'm sorry. I'm told...I was hedging. I'm told it was technical material in water, diluted in water, as a...

DR. STINCHCOMB: As a solution or a slurry?

DR. LAMB: Slurry.

DR. STINCHCOMB: Is that typical of other studies of this type, to put it in a slurry or not?

DR. LAMB: Yes.

DR. HEERINGA: Dr. Montgomery?

DR. MONTGOMERY: I thought this compound...this is Cheryl Montgomery. I thought this compound was insoluble in water?

DR. LAMB: That's why it was a slurry.

DR. MONTGOMERY: I understand that, but if it's in a slurry and it's in water...oh, I guess I'm ...I'm obviously confused. I understand it's a slurry in water. You're saying that this...this is basically an active ingredient...

DR. LAMB: That's essen...

DR. MONTGOMERY: It's insoluble in water, so it's not in a...not.

DR. LAMB: And that is how it's used.

When it's entered...put in these tanks, water is added, and Jeff knows more about this than me, but that's...it ends up being used, actually, and the worker exposure actually is to a slurry in water. So, that is a clear reflection of the product as a worker is going to...if a worker comes in contact with it, that's what they'll come in contact with.

DR. MONTGOMERY: Is this part no-liquid formulation?

DR. LAMB: Don Carlson will answer that one.

DR. MONTGOMERY: And it comes in drums. Typically...

DR. HEERINGA: Dr. Carlson?

DR. MONTGOMERY: ...chemicals that come in drums are in liquid formulation, and if this compound is insoluble in water, it must have surfactants added to keep it suspended so that it can stay in the solution.

DR. CARLSON: Don Carlson, FMC Corporation again. First off, let me address the question of the water solubility. The water solubility of carbofuran varies anywhere, in the figures that have been made available, from about 340 ppm to 600 ppm, so it's not a...a relatively insoluble material.

In regard to the formulation, the technical material for the furidan flowable was very finely ground. It is put on a very finely ground clay carrier, and then, that is suspended in water. The water is about 40 percent of the formulation, and there are suspending agents in the...the formulation that help to keep it in suspension.

DR. MONTGOMERY: I'm going to think on this.

DR. HATTIS: Was there suspending agents also in the technical material that was used for the experiments?

DR. CARLSON: The experiment was done on technical material. There was a slurry of the technical material which was pasted on or, you know, applied to the skin, spread on the skin.

DR. HATTIS: It did have the suspending agents. Is that right?

DR. CARLSON: No.

DR. HEERINGA: Dr. Carlson answered that.

DR. CARLSON: The answer was no.

DR. HATTIS: Thank you.

DR. CARLSON: You're welcome.

DR. CUMMINGS: Dr. Heeringa, could I

just add?

DR. HEERINGA: Dr. Cummings, sure.

DR. CUMMINGS: Just for...just for clarification, the...the guideline study from the USEPA is to use...is to use technical material and not formulated product.

DR. CARLSON: If I may, to further clarify...

DR. HEERINGA: Sure, Don Carlson.

DR. CARLSON: ...in relation to Dr. Hattis' question, what was used in the study was the technical material in a slurry, and what the guidelines specify is the technical material to be used in the study.

DR. HEERINGA: Thank you. At this point, we have, with the presentation by FMC and the worker exposure assessment, there is supporting papers and reports that we've received. Any additional questions of clarification before we move on?

(No response.)

DR. HEERINGA: Not seeing any...one more.

DR. BUNGE: Annette Bunge. One of the issues that's been raised was that other 21 or 28-day dermal tox studies for other carbamates or...or

organophosphates have been used, but what the Agency has said about this pesticide is that it has this very rapid recovery, and so, that's my question. On these other pesticides that have...where studies have been accepted, was the recovery as...as similarly rapid?

Because it's not just a combination...it's a combination also of how quickly the body is able to clear them.

DR. LAMB: I think it would not be true for the organophosphates, because the binding is typically irreversible, but for the carbamates, it would be, but they typically have much shorter half-lives, and, in fact, I think EPA talked about that earlier this morning as far as the...the range of half-lives for the N-methyl carbamates.

DR. HEERINGA: Okay. Well, thank you very much, Dr. Lamb and Dr. Driver. Stick around. You may be up here again shortly, I believe.

At this point, I'll turn back to Dr. Cummings. I think we're up for the presentation on the human health and dietary risk assessment.

DR. CUMMINGS: It will just be a moment while we switch...

DR. HEERINGA: Absolutely. Before we begin, I want to...just a small administrative matter.

Mr. Larry Kleingartner, if you would be willing to, speak to Sharlene at some point.

Thank you very much for your patience, and at this point, we'd like to begin, and, Dr. Lamb, if you could begin and introduce your colleagues, as appropriate.

DR. LAMB: You bet. With me today...again, I'm Jim Lam of the Weinberg Group. I have Dr. Robert Sielken who will be speaking after me, and then I'll speak again, and then Dr. Morris from FMC will speak on the dietary exposure model. So, you're going to get four relatively short presentations. We're trying to help you get through the lunch down and keep things rolling along. How is that?

I will start with the oral risk assessment. Some of these points we may have already covered. If we have, I'll move along as quickly as possible to try to help you get towards schedule.

The outline of our presentations, initially, I'll talk about how FMC and EPA have done their risk assessment generally and the selection of a point of departure and past practice. Then, Dr. Sielken will speak to the mathematical and statistical issues. I'll talk again on some of the specific toxicological points and conclude this section, and then Dr. Morris will

talk about the dietary exposure assessment that ties the risk assessment together.

I think you all know that the Food Quality Protection Act controls the presence of pesticides on foods. Both EPA and FDA...FMC have carefully estimated dietary exposure using various data and models.

But one of the key concepts in this is a discussion of the risk cup, the method...and it was mentioned yesterday. It's a...it's a model or a...a target that was developed under the Food Quality Protection Act that is a calculated allowable intake of pesticide in food and...and other sources, food, drinking water, for example.

One of the first steps and key steps in determining the risk cup is the selection of the point of departure. I am going to make your lives much simpler today by not arguing much about the point of departure.

You can do this from oral studies, whether they're gavage or dietary. You can do it with one study; you can do it with multiple studies.

Ultimately, you're trying to get a level that represents no to a low response. And whether this is a LOAEL or a NOAEL or some version of a benchmark dose, as you heard yesterday, the EPA policy, when they use

the benchmark dose, is to use the BMDL10 which is the 95 percent lower confidence limit on the BMD10.

The risk cup is a calculated allowable take...intake, because the calculation comes in once you have the point of departure, you divide it by various factors. There's the interspecies uncertainty factor, the intraspecies uncertainty factor, and the default values for those are 10. And there are the regulatorily...the legislatively mandated FQPA factor that begins at 10 and can be reduced if there's sufficient data to protect children.

EPA, for carbofuran, has selected a point of departure of 0.3 mg/kg based on postnatal day 11 rat brain acetylcholinesterase. Those are the data upon which they're relying on, but they have a concern about, obviously, acetylcholinesterase inhibition. That is one of the major issues that we will be talking about, because that, in turn, leads to differences in uncertainty factors.

They...the 10 and 10 standard interspecies and intraspecies uncertainty factors are used, but they drop the 10-fold FQPA to 5 instead of what we think should be 1, and you'll hear me and EPA talk about the risk cup. We're referring often to this acute population-adjusted dose that Jack Housenger mentioned

yesterday or an adjusted reference dose, adjusted by the FQPA factor.

What are the differences? Well, the differences are, actually, substantial, and they really come down to a couple of issues. There's no argument about leaving the intraspecies factors at 10. There is some...going to be some discussion about the interspecies, whether it should remain at 10 or might be dropped to 3. There is major issue about the Food Quality Protection Act factor which, currently, EPA has at 5 and we strongly believe should be at 1.

And in the end, that leads to differences using exactly the same brain PND11 acetylcholinesterase endpoint for us and for EPA. The...the risk cup for EPA is 0.00006 mg/kg/day, and the way we do the calculation with an uncertainty factor of 300, it would be 0.001. If you used 100, it would be 0.003. I'm sorry, 30 or 100 are the two uncertainty factors we think are...are...it's going to be somewhere...it ought to be somewhere in that range.

As I mentioned, to me, it takes a lot of the...it should solve some of the discussion we've had for this. For the purposes of this study, of this evaluation, the brain acetylcholinesterase from PND11 of 0.03 is the number that FMC is using for the risk

assessment. It's the uncertainty factors that matter, because it shrinks the risk cup down by to 5 to 16.7-fold.

With EPA's factors, nearly every use of carbofuran is precluded, and without them, the risk cup allows the continued use of carbofuran with the lab...adjusted label, as we've already discussed.

So, that additional risk factor or uncertainty factor is very significant. If you use the smallest uncertainty factor, you get the largest risk cup. The 100-fold gets you another, and the 500 shrinks it down quite a bit, and I can't tell you whether these are quantitatively correct cuts or not. I'm sure they are, in fact, though.

We're using the pup brain acetylcholinesterase endpoint, and EPA has expressed the concern that I know you've heard that RBC acetylcholinesterase is up to 5 times more sensitive than brain. We...we...they've used the BMD50 calculations to make that comparison of sensitivity rather than individual animal data.

The details on that calculation are not apparent to us. The assumptions, the calculations, the data, we can't find the in the Notice of Intent to Cancel. We can't find them within other Agency

documents.

I know that you've already heard that the number has changed a bit with a recalculation. We don't know how that calculation was done, either, but I think we're getting closer to understanding the numbers.

Bottom line is we believe that the use of pup brain acetylcholinesterase as the point of departure is the appropriate. It is an...we are talking about an acute effect. We are talking about a...an acute response, not a chronic risk.

As EPA indicated yesterday, you don't have issues of carcinogenicity, reproductive, developmental and neurotox. The brain acetylcholinesterase, again as mentioned yesterday, is the adverse effect. This is an effect that's been measured in juvenile animals, and it models nervous system responses.

The biological basis for some of these issues I'm going to talk about after Dr. Sielken gets through, but...but you should go into this knowing that we agree on one uncertainty factor. We're closer on a second, the interspecies factor being in the range of 3 to 10. We completely disagree on the FQPA factor being 5 and think it should be closer to 1, it...in fact, it should be 1.

So, the uncertainty factor really belongs in that range of 30 to 100, not 500, and we're going to talk about each of these in more detail.

One point I want to make that I alluded to earlier is this chart that we've seen several times in this point as the origin of the 5-fold FQPA factor. These are data from adults. These are data that were shown in the MMC cumulative risk assessment, and this particular data point that's circled is the one that, actually, FMC had identified that as erroneous.

The way...we believe that number is low simply because it's an artifact of a combination of studies, and, ultimately, in the SAP issue paper, basically, EPA says, and we agree, that the BMD10s for adult RBC and brain acetylcholinesterase are similar, and they don't support the 5x factor used for adults that used...based on the adult data in the 2006 risk assessment.

That is...that is how they say it started, but we agree that then...it started with a concern that adults were different, and it turns out they're not. And this is the position with EPA is agreeing with in the document.

So, I think it's important to clarify, because I'm fearful you may have misunderstood

the...the point of that N-methyl carbamate slide and comparing aldicarb to carbofuran and other N-methyl carbamates.

So, now I'm going to move to the math. The bottom line here, though, is that the 5-fold FQPA factor is being applied because of the lack of RBC acetylcholinesterase data in juvenile animals at the low end of the dose response curve.

I'm going to put the pots aside for now and let you listen to Dr. Sielken in the meantime and the mathematical points.

Thank you. And, as usual, hold questions till we're all done.

DR. HEERINGA: Yes. Dr. Sielken?

DR. SIELKEN: All right. This is Bob Sielken, and I was asked to do a statistical comparison of acetylcholinesterase inhibitions in RBC and brain in rats exposed to carbofuran, and as Dr. Lamb has indicated, we're going to be talking about the juvenile rates, the PND11 in the EPA study, the PND17 in the other EPA ORD study. So, we're going to be looking at those juvenile rats, and we're going to be looking at the relevancy of sensitivity of RBC to brain.

And when we come back, Dr. Lamb will go back to the issue about well, we probably don't even need to

be looking at RBC, because brain is the relevant endpoint. But because this issue of the 5x has come up about the relative sensitivity, then let me try and address that and really put that to bed, because there really isn't a substantial difference in sensitivity between RBC and brain in those juvenile rats.

EPA's methodology for comparing these cholinesterase values is indicated in their issue paper as being derived from table 5, and this is a reproduction of table 5 shown here on this slide, and in table 5, they actually tabled BMD50 values for PND11 in brain, 0.23; BMD...BMD50 in PND11 rats at 0.05 for RBC.

Then they took the ratio of those two numbers, 0.23 divided by 0.05, 4.6. Did the same thing for PND17 animals, and said that on this basis, they're going to conclude that RBC is...the juvenile rats are 3 to 5 times more sensitive to RBC inhibition than they are to brain inhibition.

There are a couple of issues that I'd like to talk about concerning their methodology. The first is the derivation of the numerical values in that table 5. It's not transparent. The numbers cannot be confirmed, and in fact, yesterday, EPA said they've changed at the last minute.

So, I...I do want to...to look at those numbers. I think the more important issue, though, is...is not where those PMD50s came from, although we can't reproduce them in the table as it is. The more important issue is that you have better data for looking at relative sensitivity than those BMD50s. BMD50s might be used if you didn't have better data, but here, you really do have better data.

You, in fact, observed RBC and brain inhibitions in the same animal at the same time. So, I mean, you have individual animal data. That's being ignored, the simultaneous availability of RBC and brain in the same animal that's ignored in the BMD calculation, and, really, you can use it directly to get a better idea of relative inhibition.

And that would be in...sympathetic to the comment we heard earlier from EPA that there is a high degree of intra-animal correlation, that within an animal brain and RBC are correlated. That correlation is lost when you ig...ignore the individual animal and you just spread the RBC values in one calculation and the brain values in a different calculation. Okay.

Most of you, in fact, all of you probably know what a BMD50 is. Here, since we're looking at a continuous endpoint, cholinesterase inhibition, we're

starting with a curve where we've got 100 percent of the acetylcholinesterase level in the controls, and we're looking for how that level decreases as the dose increases. And the point where the acetylcholinesterase level is decreased 50 percent, the dose corresponding to that is the BMD50. Simple idea.

If you look at the PND11 values from the EPA ORD study, Moser, in 2007, and you plot that data as I have done here, the diamonds, if you will, in this plot indicate the sample means. I could have put on here sample standard deviations as well, but for the purposes of this talk, the means will be fine. They're showing the mean inhibition at...at the experiment...at the five experimental doses.

And you'll notice that...and this is for RBC. And you'll notice that for RBC, the point where you have a 50 percent inhibition happens to correspond to that lowest experimental dose, 0.1 mg/kg/day. So, regardless of the modeling or anything else that's done with this data, if you're looking for the point where there's 50 percent inhibition, you can go directly to the experimental data, and it should be 0.1. Anything else is, you know, not reflecting the experimental data.

EPA got 0.05 initially. They got a different

number yesterday, but they got 0.05 in their report, perhaps suggesting that you need to look at the data itself, not just reported numbers supposedly related to the data.

For PND17, the top curve here which is blue but it's on top, is brain. The one underneath is RBC. And this is, again, a plot of experimental data. You can see, again, for RBC, that there's 50 percent inhibition at the lowest experimental dose. So, again, the BMD ought to be around 0.1. EPA got 0.07 in their calculations initially.

You look at brain. Well, it's almost down to 50 percent at the second dose, 0.3, so maybe the BMD is just a little bit bigger than 0.3. It's certainly not 0.2, as was in EPA's table 5.

This discrepancies between the data and...between the experimental data and the numbers in EPA's table 5 made it hard to reconcile what was EPA doing to actually get those values and come to their conclusion. Okay.

Again, with the idea of emphasizing looking at the experimental data, if you just look at the two lowest experimental doses in this study, EPA's study in the PND11 pups, at the lowest dose, 0.1, the ratio between the reduction in RBC and the reduction in brain

at that lowest dose is 1.3, not 5. It's 1.3.

You look also at the ratio of the percent reductions at 0.3, the second lowest dose, and the ratio is 1.2, again, not 5.

If you want to do dose response modeling here...and I am a dose response modeler by trade, so being...being a little disparaging about the dose response modeling comes from one who does it all the time, too, but I never do it without looking at the data. Okay? So, if I go back to that PND11 data for brain in the Moser study, the data points are here.

A fit of the exponential model with the power in the model being 1 or a fit of the HAIR model which is like a McCayliss-Menton model, those models, either one of them, fit this data reasonably well. The same thing could be said for the RBC data, particularly when you're looking at the lower end.

I've done a piece-wise linear plot, but I'm really trying to emphasize here that at the points where you have data, these fitted curves go close to the experimental data, and you can pick any of the...either of those two models.

If you want to go with a BMD approach...and, again, I don't think that that's the best approach...you can take either one of these fitted

models, the fitted exponential or the fitted HAIR model. both of which fit the data reasonably, and look at BMD10s, BMD20s, BMD30s, BMD40s, just depending on how far back towards zero you want to do your extrapolation. Or you can do it linearly which is probably the closest thing to the data.

And any of those numbers, comparisons of BMD10s, 20s, 30s, 40s, using linear extrapolation fitted exponential, fitted Hill models, those ratios of relative sensitivity in doses...in the dose metric come out to be all numbers less than 2. Certainly, well less than 5.

Okay, I indicated in the beginning that there was an issue with how EPA derived its numbers and it was hard to replicate, et cetera. If you go ahead and take their approach, you do show, if you enter it correctly, that regardless of which model you take, you're looking at relative sensitivity less than 2-fold, more like 1.5-fold. All right?

And I also indicated at the start that there was a better approach. You've got data on RBC and brain in the same animal. So, why not use that data?

And that's true not only of the Moser studies; it's true of the FMC studies as well. We might debate about whether their RBC values are usable

or not in those FMC studies, but it's always there. That's the protocol, is to observe both of these things in the same animal.

Having this information in the same animal allows for a direct comparison. You can do a...we can take advantage of or not distort the analyses by the fact that these observations on RBC and brain inhibition in the same animal are highly correlated.

Use of the individual rats as unit of analysis invoy...avoids issues of variability between the animals in their response, differences in dose administration, absorption, time from dose administration to observation. So, all of those differences between animals are kind of eliminated or, at least, better taken account of by looking within the same animal.

You don't have to make any unvalidated assumptions about the shape of the dose response models, and you don't have to dissociate the RBC data from the brain data. You don't have to treat those data sets as separate data sets.

And although this figure is a little hard to read, as a statistician, I feel compelled to show how I did my calculations, and this is an excerpt from the Moser data on PND11 pups. We have the individual

animal data, as shown by the ID numbers down the left-hand side, and for each animal at each dose level, I've got a separate reading for brain and RBC cholinesterase inhibition.

For the controls, I can take an average value to give me a reference point when I look at inhibition relative to controls.

For each of the animals, individual animals, pups, at each of the doses, I get an observation on both brain and RBC, and I can take these individual values, compare them to the control average, and get a percent reduction in, first of all, brain in that animal. And we do the calculation again comparing the animal's value to the average in controls to get a percent reduction for RBC.

I can compare those 2 percent reductions and get a relative sensitivity of RBC to brain. And I do that calculation for each of the individual animals. If I do that, I get the averages of these individual animal measurements of relative sensitivity to be these numbers at the four doses in that experiment, an overall average of around 1.2.

The specific number doesn't really matter. The numb...the important thing here is that it's really close to 1. It's certainly not 5.

I did the same calculation for the PND17 rat pups. Again, that's the other EPA pup study. And the average there is around 1.56, again, certainly less than 2, considerably less than 5.

Now, EPA raised the issue last night in the waning hours of the day that...that I was...and they knew from my advance submission that I was going to talk about this, and they were trying to find an argument against it or, at least, the scientific critique, however you want to phrase that, and they were...wanted to say that well, I'm looking at relative acetylcholinesterase values and not relative doses.

Well, my contention would be...and we have thought about this in the beginnings...is that as long as the dose response relationships are linear...and most non-threshold dose response relationships are at least approximately linear, in general approximations in the low dose region, that as long as you have roughly linearity in the low dose region, the relative reduction in the acetylcholinesterase values and the relative magnitudes of BMDs are equal.

And I'm a mathematician, so I like to do it one way, but I thought the easiest thing for my clients and probably the panel was just to do a hypothetical example that was some pictures. And so, I did.

Here's the acetylcholinesterase values for brain in blue and in red is RBC. Other than the fact that brain was usually bigger than RBC, the...that's a hypothetical example. They have different slopes in those linear relationships.

If I put that back and draw the picture in terms of fractional reduction, you'll notice that when I did my calculations, I did it not on fractional reductions but acetylcholinesterase values, but if I draw the pictures in terms of fractional reduction, I get that picture.

And if I go ahead and do the comparison of BMD50s, say, if I just, you know, come over from 50 percent and identify the two BMD50s, 2.3 and 3, take the ratio of those, that ratio in this picture is about 1.3.

If I do the...if I look at it the other way, that is, I look at a dose and look at the relative acetylcholinesterase values, then that's what I get in this picture. But if I take a dose of, say, 0.3...I mean, 3...and these are an arbitrary dose scale...3 and go up, the fractional reduction for RBC is about 0.65. The fractional reduction for brain is about a half. The ratio if those two reductions is 1.3.

So, whether you want to look at this in terms

of acetylcholinesterase values or BMDs in the low dose region, the comparison is the same or equivalent.

For those of you who like algebra better than pictures, your slide sets show that this equivalence holds from an algebraic point of view as well as a pictorial point of view, but I'll skip those slides for everyone's benefit and just go right to my conclusions.

And the conclusions are that comparisons of RBC and brain sensitivity to inhibition are scientifically and statistically most valid when done on an individual pup basis when that data is available, and it is available here. EPA's approach of relying on the BMD50s and basing the comparisons on these artificial constructs requires unnecessary assumptions about the dose response, and it loses the commonality of RBC and brain within the same animal.

The average ratio of RBC to brain in the PND11 pups which is our target, PND11 pups, is 1.22 which really is not a biologically significant difference, as being told to me by my biological colleagues. So, you're really looking at 1.22. You're not looking at 5. You're not even looking at 2. The FQPA safety factor really should be 1, and that's the bottom line.

DR. LAMB: As promised, I'll...this is

Jim Lam of the Weinberg Group. I'll move on to the...immediately to the toxicological issues and...and then pass over to Dr. Robert Morris.

First of all, we need to make the point that brain acetylcholinesterase is, in fact, the more relevant endpoint. It is more reliable statistically. The levels are higher in brain by, typically, an order of magnitude compared to red blood cells. It's more relevant toxicologically.

The brain has basically been used as the point of departure in numerous other risk assessments, and the comparison of a value of brain acetylcholinesterase to red blood cell acetylcholinesterase has been reviewed by the science advisory panel in the past.

I'm not going to read this whole slide, but the...the bottom line in the review with respect to the cumulative risk assessment was brain provide a health protective endpoint for central and peripheral nervous system and represents a direct measure of a common mechanism of toxicity as opposed to using surrogate measures which is a term that I think we've all used in describing red blood cell. It is an absolute necessity in a human study; it is not such a necessity in the rodent studies as they've been designed.

Also, within the N-methyl carbamate cumulative risk assessment, EPA's position was that brain cholinesterase is equally sensitive or more sensitive compared to RBC, and it is a health protective endpoint for both the CNS and peripheral nervous system.

It is representative of the adverse effect. It is...it is a sign of neurotoxicity. It's not a biomarker which is really what RBC may serve for. It is a functional response. RBC may or may not be a...a synch as far as a function, but it certainly is not a direct measure of neurotoxicity.

Another point made in the McDaniel study which is an ORD study published in Toxicological Sciences...and I know all these studies may be running together in your head, and I know, by now, they're actually running together in my head, but in this study, she had reviewed a number of different compounds, and in the ultimate sentence, final sentence of the document, indicated that current data supported...this is a 3007 paper...support the use of brain cholinesterase over RBC when evaluating neurotoxicity for these chemicals, and carbofuran was one of these chemicals.

RBC is variable. It's variable in EPA's

studies. It's variable in FMC studies, and this is putting aside the issue of the quality of the assay. It is much more variable than brain cholinesterase...acetylcholinesterase.

And it's less reliable. You're talking, as I said, at lower levels in red blood cells than brain. Brain acetylcholinesterase activity represents the CNS directly, and I think it better represents the peripheral nervous system than red blood cell values do.

It's...toxicologically, it is relevant. It is, in the case of carbofuran, you get a rapid response. We are talking peak responses beginning at 15 to 30 minutes. The blood-brain barrier does not seem to slow this compound down a lot once it's absorbed in the body.

The peripheral and central nervous system responses are both in nerve cell endings. They're not in circulating RBCs. As I say, one of the best uses for red blood cell is in human studies where brain is not an accessible endpoint or peripheral nervous system to map accessible endpoints.

So, in our hands, with animal toxicology studies especially, this is the best model for potential neurotoxicity. And if it is used, if RBC is

used in the risk assessment, you really need to consider the potential response at the low end of the dose response curve where you have a BMD50 comparison, but that involves unnecessary data manipulation, and it's really valid if those dose response curves are, in fact, parallel from the BMD50 to the BMD10.

The responses at the lowest levels are really the ones that are most important, and we have valid brain pup acetylcholinesterase data available at the low end of the dose response curve which is why we agree on the critical effect and point of departure.

So, in the...that same McDaniel study, the lowest dose of carbofuran...the low dose first inhibited brain acetylcholinesterase. The 0.1 mg/kg dose level, that was the one endpoint that responded. This is in adult rats.

Red blood cell and motor activity responded later. I've heard discussions of the correlation of these endpoints, but the fact is that red blood cell motor activity, brain, all tend to move together, but in these studies on carbofuran, brain moved first.

Now, we talked some already about aldicarb. You guys talked yesterday a little bit about aldicarb and urban legends. This particular example...and there's a chart over here to the...to the side

that...that is actually, it's the next slide in the package. So...so, you've got this slide, all this thing up here, but initi...comparing aldicarb in the lab to carbofuran in the rat, what you see are BMDL10s that are somewhat different, showing that there is a couple of fold, two or three-fold difference in potency based on the BMDL10s for brain, rat brain acetylcholinesterase. And I'm leaving the human and the oxamyl out at this point.

So, the potency factors for the cumulative risk assessment were in that range with a little less than a two-fold difference between aldicarb and acetylcholinesterase, but when you count the zeros, you can see that aldicarbs, APAD or risk cup is actually much larger than carbofurans.

And this chart over to the side or the one I can show up here on the top, if you put various elements at unity for carbofuran...and this is purely for the comparison...and look at adult rat brain, human RBC, BMD10, and juvenile rat brain BMD10 and compare these, aldicarb is more toxic, relative toxicity, greater toxicity, not dose. Toxicologists like me have trouble with these charts, but the toxicity of aldicarb was higher than carbofuran in every case. Oxamyl was lower, but the carbofuran's APAD is, in fact, higher

than the other two.

Another important point, talking about the uncertainty factors. If you were to take the 10 for interspecies and 10 for intraspecies, they are 100-fold results in a very conservative dietary risk assessment.

We believe that for certain purposes, you actually should consider the human study, and I realize that I may have folks throw rocks at me about this one, but the fact is the HSRB did not...you are not repeating the task that the HRB undertook. They never considered the full weight of the scientific evidence. They basically received a limited weight of evidence that has been substantially updated since the time it was presented to them.

I really believe you need to be looking at the full weight of the evidence and the human studies in context. The dermal study can be set aside, but the oral study was not excluded by the HSRB based on ethical issues. They had concerns about it scientifically which I've talked about.

The...they did BMDL...actually, EPA, I guess, did BMDL10 calculations for the human study. They are very close to...in risk assessment, close to means within an order of magnitude. They are very close to, in fact, a lot closer than that, to the 0.03 point of

departure we're talking about or effect level we're talking about for brain cholinesterase. This is a human study. Of course, this is based on the RBC cholinesterase.

Peak response was at an hour. The study was peer reviewed by several scientists who felt it was appropriate to use it to develop a reference dose.

And, in fact, EPA proposed using the human BMDL10 with uncertainty factor of 1 for interspecies and 10 for intraspecies, and that's what was presented to the HSRB, but the design of this study was limited. It was a single oral dose. It had a small sample size. There were 9 people, 2 per group. Really, the math does work.

It's...there are three dose levels. There was one control person, but each individual served also as their own control, because there was a pre-dosing evaluation was well. And the top dose was treated twice.

And then there are multiple time pre and post-dosing assessments. Bottom line is RBC cholinesterase was decreased in...in the control, oddly enough, but it was...it was decreased 11 and 22 percent at 1 hour and back to normal within 3 hours. 0.05 mg/kg did not show symptoms. And these are the data

that EPA used to develop the BMDL10.

I've already mentioned that the HSRB did not que...they were concerned about the study sample sizes especially, and I see that. That's...but, in fact, the response was very similar to the animals. You are seeing a lot of animal data, and these extensive animal studies should increase confidence in the human findings or vice versa. They, if nothing else, they reinforce that we are in the correct range for response.

You're seeing all of the data. We don't believe these human studies should be used to select a point of departure, but we do believe they can support a reduction in the interspecies uncertainty factor from 10 to 3.

Now, if you look at the dietary risk assessments, these are three different versions. The first column is the version that EPA is presenting in the Notice of Intent to Cancel. The bottom line is the acute population adjusted dose is four zeros and a 6, 0.00006, with an FQPA factor of 5 and an interspecies factor of 10.

If you did the human study, the EPA did...was silent on whether or not they would stick with 5, go to 1, or use 10, so I...but I put 1 for comparative

purposes. That's my number, to be clear.

The number for the acute POD, though, would be 0.0026. The approach that we're presenting is the same point of departure, 0.03, based on rat brain acetylcholinesterase inhibition. Same intraspecies uncertainty factor. Different interspecies uncertainty factor which has, often in this talk, been expressed as a range of 3 to 10, but the FQPA safety factor of 1 for a number of 0.001 mg/kg/day.

So, conclusions, the data converge on the BMDL10 of 0.03. Pup brain acetylcholinesterase data are reliable and, actually, in these first two bullets, I think, are entirely consistent with EPA's position. Where, I guess, we really disagree on is the additional 5x uncertainty factor based on purported sensitivity of RBC which is a surrogate measure, not an endpoint of toxicity. The brain acetylcholinesterase is the endpoint that reflects an adverse effect.

The 3x uncertainty factor based on the human data, and that the total uncertainty factors basically should be in the range of 30 to 100, not 500 as proposed by EPA, and that, basically, that...that risk assessment is much more conservative than for other carbamates or than it needs to be for carbofuran.

These are some charge questions that we have

in the toxicology. Is brain the preferred endpoint over RBC toxicologically? Do the available data support the conclusion or not that RBC acetylcholinesterase in PND11 pups is 3 to 5 times or that there's this uncertainty that it's 3 to 5 times more sensitive than brain acetylcholinesterase?

Do they support the imposition or failure to reduce the 5x FQPA factor? This is a juvenile endpoint, not an adult endpoint, and do the data support reducing the interspecies uncertainty factor to 3?

With that, we now move on to the diet, the last of this series, the dietary exposure assessment, Dr. Robert Morris from FMC.

DR. HEERINGA: Thank you, Dr. Lamb.

DR. LAMB: Thank you.

DR. HEERINGA: Dr. Morris?

DR. MORRIS: Thank you, Dr. Lamb. Good afternoon. I'm Robert Morris. I'm a risk assessment specialist with FMC Corporation, and I'll be discussing the exposure portion of the dietary risk analysis.

I...I will not bore you with what a risk cup is, because I think you've heard it more than enough. So, I'm going to move on to the exposure level and how it's calculated using the dietary eval...dietary

evaluation exposure model, the DEEM model and what that means to the actual percent of food within the dietary risk cup.

There are three critical differences between EPA and FMC's APAD calculations. This is a depiction of the two dietary risk analyses that you've been reviewing. The EPA's dietary risk analysis is a refined tier 3 analysis very similar to FMC's. The drastic difference is on the hazard side which is what you'll be determining on whether the 5x is appropriate in the FQPA side or if it should be removed and whether the 3x that Dr. Lamb is proposing is appropriate to result in an uncertainty factor of anywhere between 30 and 100.

In addition, there are a few exposure elements that would result in slight decreases in APAD that I would like to discuss. Some of them include the crops that are considered in the dietary risk analysis, and, also, there's a rather major difference between the way EPA has performed the dietary risk analysis for potatoes and residues associated with that from the PDP program and the way FMC has done it, and I will go into more detail on that.

As you've already seen, EPA considers with their dietary risk cup for their...the foods to fill

the cup over...basically overfills the risk cup, and this demonstration shows that with around 300 percent of the APAD taken up.

However, just doing one simple correction by removing the 5x uncertainty factor which has been supported by Dr. Lamb and Dr. Sielken, now the risk cup itself has plenty of room to consider not just the food but also consider rattle. So, this is an important decision that you will have to make on what is the appropriate uncertainty factor to apply.

This makes the...the decision that's facing you a very, very difficult one, and we...we really hope you get good consideration of this.

If you take only the EPA's assumptions...and this does not include any of FMC's dietary risk assumptions...and make this change, you now notice that the risk cup, which is overfilled with the EPA's assumptions, now is around 50 to 60 percent of the APAD.

As I mentioned to you earlier, the exposure...the...the crops that were actually considered in the exposure assessment for the Notice of Intent to Cancel document by EPA has additional crops that we didn't consider and for...we just considered the amended label. The amended label includes the

following crops, many of which are the exact same assumptions for residues that the EPA has. There are a couple of exceptions. Potato I'll go into in more detail, but there are a few other small slight differences between the 4F application to melons and the 15G application to cucurbit vegetables which is the way we calculate it.

The milk itself that was discussed in detail yesterday, we have the exact same assumptions that EPA has.

For potatoes, FMC has looked at a large amount of the PDP data that's available. There's nearly 3000 samples that have been collected since 1995. This is in the...this is USDA's PDP program. The...the...it's only until you get to the recent data, which is the 2006 data, though, that you see a lower detection limit.

If this lower detection limit is applied to the potato residues, it makes a drastic difference in the...the actual APAD predictions. In EPA's dietary assessment, they relied on the 2002 to 2003 LOD which is nearly an order of magnitude higher. So, when you use the EPA's practice of half the LOD, it makes a major difference in the risk assessment.

The fact that no residues have been detected

and the observation that there...there has...there are valid new samples of over 700 that have been collected makes FMC believe you should be using the most current LOD in your calculations and you shouldn't be impacting your APAD calculations on, basically, no...no residues detected.

So, if you do these corrections, you'll now see that the APAD predictions in the risk cup...and this is just 100x illustration for uncertainty factors...is in the...about a third of the cup now has been taken up by...by food contributions. This includes the most sensitive populations, similar to what EPA has considered.

If one were to take the food and then add water to it, you can see that there's room. About two-thirds of the cup is available for drinking water, and we think that once you start considering drinking water, this is...this is an area that needs a lot of consideration, because it doesn't seem like EPA put a whole lot of thought into what...what would happen if the risk cup was open and what is the relevant concentrations that should be in drinking water.

This shows, as Dr. Lamb has presented, the 300x uncertainty factor assumption, and there's even more room available for water, in this case, around 90

percent for all the dietary sensitive populations.

So, when one looks at those 100x uncertainty factor assumptions and the 30x uncertainty assumptions, one can do a drinking water level of comparison approach and see what that translates to in drinking water concentrations. This...these values that have been calculated come to between 1 and 4.4 ppb if you consider either then 100x uncertainty factor or the 30x uncertainty factor in the risk cup.

So, in conclusion, the dietary contributions from the amended label are the crops considered on the amended label, the NPORE tolerances, and the mini gran...minimal granular use all fit within the FQPA risk cup. Remaining risk cup space was then allotted for drinking water and calculated using the DWLOC approach, resulting in estimated drinking water concentrations that I mentioned that were approximately 1 to 4.4 ppb.

These numbers are actually higher than what you'll see in true concentrations found in water samples, and that will be talked about by the water panel, you know, just following this presentation.

And I have one question to pose to the panel for your consideration, and that's about when you have an ND situation like we do for potatoes and the ND has

changed because of new analytical capabilities, should the EPA be applying the new detection limit for our potato commodities, or should be...should they be using the older data?

Thank you.

DR. HEERINGA: Thank you very much. And at this point, I'd like to open it up for questions from the panel for Dr. Lamb and Dr. Sielken or Dr. Moore. Yes, I'll start with Dr. Edler.

DR. EDLER: Lutz Edler, German Cancer Center. I think...with problems with the time, but only two short questions, I think.

One question to...to Dr. Sielken. The calculations you showed of the original data where you got these factors, 1.2, 1.3 and so on, did you also consider the variability of the controls which is actually used for normalizing these data? Did you...did you do some calculations? Because if you calculate these ratios, they get a lot of variability which are not in...in...in the point figure actually.

DR. MORRIS: The individual animal data is there, of course, for the controls. I did not look at percent inhibitions relative to the control mean minus the standard deviation. I could have done that.

That would have affected...would have

affected both the percent inhibition for brain as well as the percent inhibition for RBC. I don't know how much of an effect that would have for the ratio.

DR. EDLER: May I just follow up? That's a totally different question which I have in mind for a while. Are there specific reasons that in these newer studies, the radiometric..radiometric method for the RBC and the brain con...concentrations were not used? Because I...I'm asking this also because in the 2005 SAP, there had been a discussion about that usage of these methods, and my question is simply what's the reason that one stayed with a modified Elman method?

DR. SIELKEN: This is Bob Sielken, again, to respond. The...the calculations that I showed for relative inhibition of LDC in brain being less than two-fold was all based on EPA's...EPA ORD studies, and it's my understanding that they used the radiometric method, but there was no problem in their..their analysis. That was all EPA...

DR. HEERINGA: Dr. Lamb? Sorry, Dr. Sielken.

DR. LAMB: Yeah, with regard to the Elman assay that is the one that typically is done in these guideline studies. The...I don't know that I

want to go out on a limb as to whether...you guys would probably know better than I...as to whether that is the method that...the method, only method required or mentioned.

DR. HEERINGA: We maybe could have your...Jane to respond. Have her come up and say what she said to you.

DR. MCCARTY: My name is Jane McCarty. I'm a toxicologist with FMC Corporation and was responsible for monitoring the studies that were done by FMC.

The reason that the contract laboratories that most industry goes to to do these kinds of studies aren't done using the radiometric method is that most of these laboratories do not have licenses for handling the radio-labeled material that's required in that process, so they don't have that method available to do these large studies.

DR. HEERINGA: Thank you. Dr. Handwerger?

DR. HANDWERGER: I'm just a small town pediatrician, and I...I...I'm really very surprised that neither you or the EPA have mentioned pregnancy, fetuses, or risk of pesticides to pregnant women.

You know, I think of the paper last year on

diabetes care from NIEHS, another part of the government, where Seldona and his colleagues showing an increased incidence of gestational diabetes in women exposed to a number of pesticides, including carbofuran, circumstantial evidence of an increased risk in some studies of breast cancer to women who've been exposed to carbofuran, and so forth, but we've not talked about any of...of these kinds of issues.

You know, I love birds, and I love rats and mice, but, you know, I...I...I happen to work more with people, and...and I...I really am somewhat surprised that we haven't really talked about that. We've talked about atrazine and, you know, its potential dangers for prostate cancer and so forth, but I'm also concerned about things like gestational diabetes, because, you know, it...it's said that these pesticides are not teratogens, but diabetes in pregnancy is a teratogen, and...and, clearly, women with gestational diabetes have a...a marked increased risk of having infants with congenital abnormalities and so forth.

And I know that we're not here to discuss this issue, but I just wish, when we talk about the health effects, that we...we go and look at the literature and think about what is there about...about humans and about pregnancy and about fetuses and with

possible effects of...of carbofuran on sperm counts in workers. There have been reports about decreased sperm counts on workers, but we're not talking about that here today.

I mean, of course, I don't know why we're not talking about this today, but I'd just like to...for us just to keep that in perspective.

DR. HEERINGA: I think, Dr. Lamb, if you want to address that question, you may. Otherwise, I think it's one appropriately put to the EPA, too, because I think the statements have been made to essentially set aside some of these other effects that Dr. Handwerger is really alluding to.

DR. LAMB: I think...I think it's the disadvantage of where you are in this process which is the process that involves hundreds of other toxicological and exposure studies and...and these issues have...are not ignored. They are addressed at other studies along the way, both in the initial registration, re-registration, and as other questions come up.

And what's happened is we're to the point that we're...we're at what is...what is typically referred in risk assessment as the critical effect. And so, these other endpoints have been addressed

either through animal toxicology studies...I mean, if something comes up in the literature, I can tell you that if it's problematic regarding a pesticide, EPA is aware of it, and we, if...if it's a product for which we're responsible, the companies respond, and I think EPA would say the same thing.

But this is...we're to the point that this is the most sensitive effect, most sensitive species. This is what we think should be used for risk assessment, and if you protect from this, you should, at the same time, be protecting from the other concerns that you...you're raising.

At the same time, I can't respond to every epidemiological observation that may be raised without some specifics. So, I'd stop there.

DR. HEERINGA: Thank you, Dr. Lamb. Dr. Portier and Dr. Chambers.

DR. PORTIER: Dr. Sielken, you fit an exponential model to your data, and if I remember correctly, EPA fit an exponential power model to the same data. Did you fit the power models, and is the power different than 1?

DR. SIELKEN: Yes, I did hear that comment from EPA yesterday. I did hear Dr. Setzer say that for the brain data, when he fit the power, it was

1 or close to 1, so...which is the same power that I was using.

My experience with the power model which ends up being four parameters and five data points is that that power is very volatile, variable...pick one...and hence, the results are very problematical for interpretation.

The ones that I used were...was simple exponential as well as the simple 1 model.

DR. PORTIER: But you get great fit. Right?

DR. SIELKEN: Sufficient for BMD calculations, yes.

SPEAKER: Well, I guess I have a similar question...

DR. HEERINGA: Whoa, whoa.

SPEAKER: Oh, I'm sorry.

DR. HEERINGA: Dr. Lu?

DR. LU: Alex Lu. I had a similar question. If we can go back to slide 21, okay, so try to make sense of this graph. When there's no dose, there's no inhibition, but when there's a dose 1 which is highest dose, inhibition is actually the lowest.

So, there's some sort of...am I interpreting this graph differently than you? I look at this...

DR. SIELKEN: Well, okay, maybe your...the label up there is percent inhibition relative to controls is a slightly misleading. It's a scale from zero to 1. At zero, there is no inhibition...there is not 100 percent inhibition, so you might want to label that as 100 minus the percent inhibition.

So, yes, clearly, at dose 0, there's no inhibition relative to controls, and at the highest dose which is the right-hand side of the figure, there's...

DR. HEERINGA: You want to fit the y label on there.

DR. SIELKEN: Yeah.

DR. LU: I've got a second question that's kind of related to what Dr. Portier just asked, is if we try hard to do a semi log plot, it's similar to one of the plot that EPA gave yesterday, the relationship between dose and response become very linear which sort of like you agree that the dose and response in this case should be linear. So, if you calculate BMD10 or 50 places on the curve that you present here, so my question is that, will that be...will the outcome of the calculation be the same when you convert a graph to some more linear scale and

then you can do the comparison?

So, I mean, you don't have to answer the question right now, but I suspect that there is going to be some differences, and the differences will probably be in between your calculation and the Agency's calculation.

DR. SIELKEN: I don't think so. I think you're point is...is a good one about...about scales and models, but I get the same relative sensitivity whether I'm doing...directly looking at the experimental data at the doses that were observed of 1.3, for example, as a relative sensitivity at 0.1, the experimental dose, no modeling involved versus if I do extrapolations to the low dose region and whether I go down to a BMD10, 20, 30, 40...you know, obviously, 40 is less extrapolation, but over that whole range of 40, 30, 20, 10, I'm still getting the same ratios of BMDs in the neighborhood of 1.5.

DR. HEERINGA: Dr. Ed...oh, Dr. Lu, a follow-up?

DR. LU: I do have a follow-up. I guess based on my experience with acetylcholinesterase inhibition is you don't need to get a linear response, because you always see...especially for a carbamate is that you always see a quick inhibition and then you pot

belly, and that's...that's sort of the data that kind of common out there.

If you don't put it in a somewhat, a semi-log scale, then you never get the linear range that you got to forward, and the...I think that the down side of not using the semi-log is that you ignore the effect if the dose is very low, and I think EPA has approached it sort of like a method by the area and do the calculation of the ratio, but I think my suggestion is that for you to go back and come up...do the semi calculation that EPA used and see whether there are some differences in terms of a numerical value, and you'll be surprised that...now, we're talking about ratio between 1.5 to somewhere, that 4 point something that EPA used, but I think the ratio will be very...

DR. SIELKEN: I disagree that I would get any number close to the number that 5 per EPA. I mean, I'm running the same models that they're running, and...and I just don't get anything like their ratio. And the data itself aren't suggesting that ratio.

Your other point about the quick recovery and how long it takes, that relates to the time course, and here we're looking at a fixed time which is mainly 40 minutes in the ORD. So, I don't have that time issue, because it's a fixed time.

DR. LU: Thank you.

DR. HEERINGA: Thank you, Dr. Sielken. Dr. Edler?

DR. EDLER: No, thank you.

DR. HEERINGA: Okay. Dr. MacDonald and then Dr. Chambers.

DR. MACDONALD: Yeah, I have been puzzling over these same graphs as Dr. Lu has been, and just one further question. You had together a hypothetical example that you got linearity on linear-linear scales, yet most of the graphs like this I think we have seen of the experimental data, we've got a log linear plot. So, how do you justify getting the straight line on linear-linear?

DR. SIELKEN: This is Dr. Sielken in response. I did the...I did the approach both ways. In other words, I did it on the dose scale by...by looking at the Hill models, the exponential models, and looking at it on that scale. On the relative values of the acetylcholinesterase inhibition, the inhibition scale, if you will, then those two are equivalent when I have linearity. They're not equivalent when I don't have linearity.

My contention was that line...and...and that's all that these pictures were, was to show that

when you have linearity, looking at it on the dose axis or on the response axis, you get the same ratio. That was the only purpose of these pictures. So, I mean, that's why these pictures were put up there this way.

I also made the comment that if we had approximately low dose linearity...and we are dealing with low doses in the risk assessment, not these doses. We're dealing with much lower doses....that at those low doses, the changes are going to be roughly linear.

And so, I'm talking about the right units for that type of dose scale.

Thank you.

DR. HEERINGA: Dr. Chambers?

DR. CHAMBERS: Clarification for Dr. Morris, please. This is Jan Chambers.

When you're talking about the LODs changing because of the newer technology, and you talked about the number of samples, were you just looking at the more recent samples since the technology got more precise?

DR. MORRIS: Robert Morris in response. I was looking at all the data, but I was applying the limit of detection from the new analytical capabilities, the 2006 data.

DR. CHAMBERS: But applying that to even

the older data that might have used the older technology?

DR. MORRIS: That's right, because you...you can't...when you do the residue definition files, you can't have mixed amounts in your...in the file.. You have to have one or the other for LOD.

DR. HEERINGA: Yes, Dr. Stinchcomb?

DR. STINCHCOMB: If it's not inappropriate, can I ask one more question about the dermal study or not?

DR. HEERINGA: Why don't you...because we're going to turn to water next and...

DR. STINCHCOMB: Okay.

DR. HEERINGA: ...I think let's go ahead and get your question in.

DR. STINCHCOMB: So, when the slurry was applied to the skin in the dermal tox study, is there significant water that's still remaining, or is the water all rubbed in and there was just dried particles on the skin? And then, what happens at 6 hours when the occlusion covering was removed?

DR. LAMB: I think that originally, it's there as a slurry. It's...it's placed there and that, over time, I think, with most of these studies...I am not familiar with this...what they saw in this

particular case, but in most of these studies, the application site dries, and that at the end of the application period, this is why you then clean out that site, and I think they used Ivory soap and water, basically, to clean the site and then immediately sacrificed the animals.

So, it's put on wet, but it has access to air, so my expectation is it would dry over time.

DR. CHAMBERS: This states that there was occlusion. Is that not true?

DR. LAMB: I thought it was semi-occlusion. Let me check with Dr. McLean. Semi occlusion, meaning it has access to air, but the animal can't reach it.

DR. CHAMBERS: So the water evaporates and you have dried particles?

DR. LAMB: That's my guess, yes.

DR. CHAMBERS: Do we know the particle size of the chemical?

DR. LAMB: I don't. Somebody might, but I don't.

DR. HEERINGA: We can probably get that for you.

DR. LAMB: Yeah.

DR. HEERINGA: Yes, Dr. Bunge?

DR. BUNGE: Can I just make one follow-up question?

DR. HEERINGA: Sure.

DR. BUNGE: So, the tape that's used, is it non-occlusive? That's the two 3M tapes that are talked about, are they...can water go through them?

DR. MCCARTY: Jane McCarty from FMC. The tape that they used to cover the site, first they put, I think, gauze on, and then they put vet wrap which is a...a semi-elastic, semi-occlusive wrap. It was not a totally occlusive wrap.

Even though I think the EPA DER described it as an occlusive covering, it was not totally occlusive. It was always semi-occlusive.

DR. HEERINGA: Dr. Reed?

DR. REED: With...excuse me. With all the questions that, the follow-up questions that we have, I guess we're, at least we are, curious about the concept of...of the entire amount that is applied to the skin in terms of...of how much is...is...is it in contact with the skin. Is it the entire amount whether it's in...in a solid form or...or wetable? I think there was mention about solubility.

So, can you give us an estimate in terms of how much was in contact with the skin that was in the

wet stuff?

DR. LAMB: What I can do is provide for you the area that was treated on the back of the animal that...that will answer that question. It is in the report, and we can pull it out so that you know, and the, basically, the volume of the material so we can calculate that.

So, is that in respon...does that answer your question?

DR. MCCARTY: I can answer the area. The area is...

DR. HEERINGA: Dr. McCarty?

DR. MCCARTY: Dr. Jane McCarty. The area that the material is applied to 5 by 8 cm, and the material was prepared. It was a slurry. The water was added to the weighed material, and that slurry was applied and spread over that 5 by 8 cm area.

DR. REED: As a follow-up...this is Ruby Reed again. And so, I guess the curious question is...is how much is taken up by the gauze and then, you know, dry up at what point so that how much of the chemical is in contact with the skin after 6 hours. Does that make sense in terms of...

DR. MCCARTY: Yeah, I don't...I don't have any way of measuring that. I don't know.

DR. HEERINGA: Okay. What I'd like to do at this point, here is my proposal which I'm going to follow. It's...chance to vote was yesterday, I guess, and I'm sorry about this, but I feel it's very important to finish this series of presentations this evening.

What I'd like to do is I'd like to call for a 10-minute break, and then, as a service, we're going to have Larry Kleingartner from the Sunflower Growers is going to do a short presentation, and then we will move to a full consideration of the...the water presentation by SM...FMC. So, is that okay?

I anticipate wrapping up by 7:00. The only thing that we have to make sure of is that I'm told at 6:00 p.m., these doors lock out here, so if you...if you want to use the facilities, you're going to need a...a hall monitor to let you back in.

(WHEREUPON, Session C was concluded and a brief recess was taken.)

DR. FAWCETT: My name is Richard Fawcett, and I am one of the panel of 3 that FMC convened to conduct a refined risk assessment for Carbofuran in drinking water, and to also recommend mitigation measures to protect ground and surface water. The other members of the panel are Burnie Engel

and Dr. Engel, and Martin Williams. Robert Morris is also with us here from FMC, and may be able to answer some questions.

I want to start with just a little cheat-sheet here with some acronym definitions. We may use these, and hopefully we'll define them the first time that time that we get to them, but if not, you'll have this in the materials you can refer back to. I want to introduce this topic by very briefly summarizing EPA's methods and conclusions on drinking water exposure, and contrast those with those from the panel that we have here, that will be speaking to you this afternoon. In their tier 2 modeling process EPA used their typical procedure of the index resovoir modeling, using Prism's exams.

But some important assumptions that were made is that 100 % of the crop or in some cases all of the agricultural land was treated with Carbofuran. So that meant that up to 87 % of the watershed received Carbofuran. Using those modeling techniques, they calculated acute estimated drinking water at concentrations of from 19 to 49 part per billion. In their ground water assessments the estimated exposure by scaling results from a shallow ground water perspective study in Maryland to reflect all crops

specific application rates in all uses across the country.

Using that technique, their 90 day average estimated drinking water concentrations were from 1.4 to as much as 110 part per billion. Now I am sure you are all familiar with the EPA's tiered approach in risk assessment. Where they begin with a screening level, and then may go to higher tier, more detailed assessments, if that's deemed appropriate or necessary. EPA stopped at the tier 2, and one of the reasons they did is because as you've seen in EPA's calculations, the risk cup was full with their dietary assessment.

There was not room for drinking water, so it was deemed not necessary to carry forward with some higher-tier assessments. However, they do in their procedures allow for this, and the quote on the bottom of the screen simply says, "failing a tier however, does not necessarily mean that the chemical is likely to cause health or environmental problems, but rather there is a need to move to a higher tier, and conduct a more refined assessment."

And because, with the material you have seen presented by FMC would indicate that there is room in that risk cup, then we think it is very appropriate that we need to have the best assessment possible to

know what that drinking water contribution would be, to see if there is room in that risk cup. And we would argue that there is room, as you'll see from our calculations. So we will be giving you the results from that higher tier, a some refined assessment, this afternoon.

We have already heard - and I am going to try to be as brief as I can - You have heard how the use of Carbofuran has changed over the years, due to market forces and changes in label directions and eliminations of some crops. The slide on the left shows 1992 us of Carbofuran going from the lighter colors through green to blue is the highest use. In 2005, you can see how the use has declined considerably. And because alfalfa is no longer on the label, the 2005 data has been adjusted for that. If you were to consider a pre-emergent herbicide such as Atrogene, which is used on 80% of corn acres, or may a post-emergent herbicide like Glyphocate that is used on over 90% of the soy beans, then it is very appropriate to assume that 100 % of the crop is treated with that product. But for something like Carbofuran, when less than 1 % of the crop area is treated, that really is not appropriate. And it's an important concept that we're going to be talking about, considering that percent of crop

treated. Just to very quickly summarize what you'll hear about our surface water assessments, FMC in their tier 3 modeling, a higher tier modeling, considered the actual percent treated for Carbofuran from sales figures. And for the watersheds a model that was anywhere that was form 0.41 percent of the crop area treated.

And that translated into from 0 to 0.7 % of the watershed treated with Carbofuran. In that modeling you'll see the results that presented later, that shows that the estimated drinking water concentrations were less than 1 part per billion. EPA, as it turns out, has also used that tier 3 approach and they have used the percent crop treated approach, in the cumulative methyl carbonate assessment, using that procedure they came out with as well with concentrations below one part per billion.

For ground water, the FMC's tier 3 modeling analysis also showed that Carbofuran's concentrations would be expected to be below 1 part per billion. And the monitoring data that we'll be showing are also supportive of that tier 3 modeling estimate. I would like to turn the slides over to Dr. Engel, who will be reporting on some of the surface water assessments we've conducted.

DR. ENGEL: Hi, I am Doctor Engel, I have extensive research experience with hydro logic water quality modeling, and large spacial data sets to support those analysis. I'll spend about 10 minutes talking about a portion of the surface water assessment, initially looking at some of the work that we did with resovoir based systems, and then pass the slides to Marty Williams, who will talk about the flowing water assessment.

For the surface water assessment, we looked as resovoirs within Indiana, used the Prism Exams Model - for which I'll provide a couple of more details in a couple of moments - and a key point that here is that we used actual Carbofuran use within those watersheds and those assessments, and you'll see the impact that has. We then looked at a national resovoir assessment to understand what the potential vulnerability may be for resovoirs nationally to Carbofuran use, and considered the community water system characteristics in that analysis. And finally, as I said, Marty Williams will talk about the flowing water assessment, the rivers that may be used for community water systems, and used, monitoring data used the warp model that he'll describe briefly and some statistical analysis in that exploration.

First, let me do a quick overview of a couple of key concepts in setting up this resovoir modeling approach that we have used, and that EPA has used as well. As you are probably aware, there is some watershed area that would contribute run-off to a resovoir, so that might be depicted here, and would be called the drainage area. So this is going to be the area on which materials may be applied, so therefore this represents a potential capacity to deliver materials to a resovoir.

Run off from that area might enter a resovoir so that would have some capacity. So depending on the size of that capacity, larger would be more potential for dilution. So sizes on these are going to matter. Not all this watershed is likely to be treated. As many of you flew across the country to get here, you probably noticed that even within the corn belt not everything is low cropped agriculture, that there are non-agricultural land uses in the watershed. So the green here depicts some percentage crop area within this watershed, and not all that area is likely to be treated with a particular product, especially a product like Carbofuran.

So some percentage of that crop may be treated, and that would ultimately provide some percent

area treated for the overall watershed. An important concept as we look at an analysis within Indiana and then scaled this nationally, was to examine this ratio of percentage area treated with Carbofuran multiplied by the drainage area of the watershed, divided by the normal capacity of the resovoir. So this combination identifies areas that would have potential for high exposure to Carbofuran or applied to other products, could be used in a similar fashion. So we'll see this again in a couple of moments.

Within Indiana, we looked at 15 actual resovoir based systems. Indiana being in the corn belt is fairly typical of land uses, soils, management practices, Carbofuran use, but importantly to us, the community water system data was available in a very timely fashion, so that we could take advantage, and use that in the Prism Exams modeling. Using the same model that EPA used in their tier 2 assessment, here though we took advantage again of actual data within Indiana, with the actual community water system and watershed data to conduct those analyses. Another important distinction here is that we used actual Carbofuran use that was experienced within this area on a county by county basis, between 2002, 2004.

What did we find? Interestingly, only 3 of

the 15 community water systems experienced Carbofuran use in that period. The percentage of application of crop areas within that was quite low, as you've heard about already, and the range of expected Carbofuran concentrations in those resovoirs ranged from .01 to 0.13 parts per billion. Contrast that to what EPA would predict with their tier 2 approach, in that same location one would get 19 to 49 parts per billion, quite a stark contrast.

I know this is a little bit complicated, so let me slow down and put some of these ratios in perspective then and explain and hopefully help you understand that some Indiana resovoirs were more potentially vulnerable to Carbofuran than the index resovoir. But at the end of the day, when we consider the percentage crop treated, that that vulnerability goes away. So let me step through this: So if we look at this top line, this is the ratio of drainage area to normal capacity for all the resovoirs within Indiana, and it ranges from about 236 as depicted here in the table, to about 2.

In contrast, the Shipman Index Resovoir that EPA has used for tier 2 assessments is about 12. So we have about half the Indiana systems being potentially more vulnerable and about half less vulnerable. If we

now modify that, and consider the percentage cropped area within those, that's going to be the second line here, we see that values reduced correspondingly and where does the index resovoir fall? It falls more at the upper end now.

If we take that one step further, and consider Carbofuran use in the watersheds now, for Indiana, since the percentages were quite low, this relationship hugs this bottom line, whereas the index resovoir remains at a value of 5.5 or 10.4, depending on the particular run that EPA was making with that. So to summarize the slide, so within Indiana, many resovoirs potentially more vulnerable, but when one considers the actual use of the Carbofuran product, they become much less vulnerable.

Again, as Doctor Williams pointed out, the EPA has in the past, in the NMC Cumulative Assessment, used a comparable sort of a concept. A watershed, some of that watershed agricultural land uses. Some of that watershed treated, some of those crop uses treated with Carbonates, and yet a smaller subset treated with Carbofuran. And if fact, Carbofuran percentages on the order of magnitude that we were using for our assessments within Indiana. When EPA did that, they found that their estimates with the index resovoir sort

of approach for Carbofuran in resovoir based systems range from .002 parts per billion, to about .82 parts per billion, that upper end being in Florida. FMC has proposed that that be removed from the label, so it we adjust that, concentrations would be actually quite close to what we found for Indiana, .002 to .35 parts per billion. And just quickly, EPA has used that concept as percent crop treated approach on other occasions.

Moving to the national assessment to understand the vulnerability or potential vulnerability of community water systems, we took the Carbofuran use between 1998 and 2003, actually we took the maximum use experienced in any county in any of those years, used the natural break method to divide this into 4 use classes, and then we go to the next slide, we use this to identify every single resovoir based systems within these class one to class four use tiers , or use categories.

We identified the potentially vulnerable community water systems in these, based on the use intensity of Carbofuran, so based on our experience in Indiana , if use intensity was more than 2.1 pounds of active ingredient per acre we put that in the potentially vulnerable category, we also looked at the

resovoir watershed property, this drainage area by percentage area treated divided by normal capacity ratio, and again based on Indiana sensitivity analysis, if that value exceeded .037, that was a good indicator that there was potential to have Carbofuran in the resovoir, above .5 parts per billion.

So we put those in the potentially vulnerable category as well, and then as one might expect, following some concerns about security of drinking water systems, we were unable to get data for Pennsylvania, and parts of North Carolina in a timely fashion. So systems for which we lacked information, we put those in the potentially vulnerable category as well.

So what are the results of that? So we found that 20 or the 30 states that we examined didn't have community water systems that were resovoir-based that were..that met any of these vulnerability criteria's, so those could be assumed to be quite safe. In the 10 remaining states we found 65 reservoir-based systems that could potentially be vulnerable, 15 based on the characteristics of Carbofuran use, or the ratio that I talked about. And again, 50 of those we were unable to obtain data. So to be conservative we placed those in this vulnerability category. You heard earlier in the

morning that FMC has proposed mitigation measures, we would propose mitigation measures for these counties in which these 65 systems would be located. At this point let me pass the slides to Marty Williams to continue the flowing water assessment.

MR. WILLIAMS: Good afternoon, or I should say good evening, at this point. My name is Marty Williams, I am with Waterborne Environmental Inc. My background is in hydrology and water quality and for the past 20 years my work has focused on the patent transport of pesticides in the environment. To address flowing water systems, we kind of took a stab at it in three different areas.

The first one was looking at the U.S.G.S. N.W.Q.A. database. N.W.Q.A. stands for the National Water Quality Analysis. It's a monitoring program developed by the U.S. Geological Survey to assess the status of waters in the country. N.W.Q.A. includes ground water and surface water data, there are study units that are not primarily agriculture, there are others that are more urban. The frequency of sampling varies. Some states cites are sampled extremely frequently, on the order of several day intervals for periods. Others are more relaxed.

That always brings people - including the

EPA- to say "was the peak concentration missed in that kind of study?". But when you look at it all together, we've got over 20,000 Carbofuran records, and that encompasses many many many site years, equivalence of data. So it is a very large data set to work with. Carbofuran, being an agriculture pesticide, you know the monitoring and analysis for that is geared mostly towards the ag type environments and the sample frequency is more geared more towards the spring and summer. So one would argue that the data on Carbofuran is bias toward where you would find Carbofuran detections. In that data there are over 20,000 records for Carbofuran, but only 71 of those samples have concentrations exceeding 0.5 ppb.

That's only 0.2 percent out of the data. The maximum concentration in that data set was 32.2 part per billion. EPA is aware of that sampling location, but it also is a very, very unique condition, it was a nursery environment with somewhere on the order of 10 pounds per acre application. That type of application is no longer labeled and allowed, and the receiving water was a very small ditch, which is not representative of a community water supply. Since community water supplies by nature have to supply sufficient water to service their population, you don't

see it on small streams, they are geared toward larger river systems.

To try to make a more, drinking water type of assessment, we took a subset of that data where we removed ditches, streams, impoundments in order to try to come up with a representative data set that was more applicable to a farm water community, water supply, and that's shown in this bottom box here. From that we still had a large number of Carbofuran records, because the N.W.Q.A. program was mostly geared towards water systems, but we only saw 29 samples greater than 0.5 ppb, and the max concentration in there was 5.82 ppb which was the Trinity River Basin in Texas, and there were only 2 or three other samples above 1 ppb, and they range from 1.0 to 2.0. This Trinity River Basin data set has been investigated by FMC in the past and, you know, if you have questions on that, Donald Carlson from FMC can come in to address it, but it also is a very unique situation.

This map shows you in the lower left the 2005 usage patterns for Carbofuran, just so you can kind of put that into context. This is the data, those are our detections. I can't see the colors from here because of my eyesight...but...it's still hard to see the colors in there. You'll find that there is very very

few points greater than 1.0 part per billion in that data set. This overlay is the non-detects, just to give you an idea of where that sampling has occurred.

The second analysis we performed was to use the U.S. Geological W.A.R.P. model, which was a watershed regression profess, which is what that acronym stands for. EPA has been looking at that as a kind of a candidate tool for addressing drinking water's exposure for pesticides And what W.A.R.P. is, is a series of regression equations developed initially for Atrazine, they later adapted it to be used for other chemicals by allowing chemical specific use intensities, half lives, and soil absorption coefficients to be used in that model, for it to be used for other chemicals.

It involves a number of spatial parameters. I'm not going to go over them in detail here, but they are using the equations because they were found them to be sensitive during their analysis in regression development. The most important one is Carbofuran use, and when you integrate those together, you get the prediction of concentrations spatially within a watershed. This shows the results of our analysis using warp.

We focused on the 4 states in the corn belt,

because they represented high areas of Carbofuran use. We did the analysis at what is called the Hot Twelve Scale watershed, which is a relatively small watershed classification is USGS's hierarchy scheme, and it's on the order of 2,500 acres in size generally. For example in Illinois there is thousands of hot twelves. So these are really, really small basins that we did the analysis on, so we are probably predicting concentrations on the high end. The colors range again from yellow low concentrations to dark blue higher concentrations.

You can see the variability in that area. The highest concentration was predicted for Illinois, and that was 0.68 parts per billion. In the past few weeks we did another analysis because EPA has expressed concern - not just for this product, but for other situations - that monitoring data does not capture a peak, and that W.A.R.P. is then giving you the range of high exposure concentrations that you might see in the typical year, rather than after some extreme events.

So we wanted to try to determine if there was a way to better estimate when an extreme event concentration could be, and to do that we did a statistical extrapolation. We took those 13,000 data points that I showed you for the river/bay systems,

filtered, they were filtered to remove the ditches and you know small streams, and canals and those sorts of systems, and we also removed all concentrations less than 0.5 ppb in order to get us that upper range of the curve of detections to fit a regression line.

We developed a best-fit distribution, and used that to extrapolate, to understand the probability of high exposure events. The red points in here are the individual detections of Carbofuran from that data set. The middle blue lines flowing from the lower left to the upper right is "best bet" line.

The outer blue lines are the 95th percentile confidence intervals. The probabilities associated with this tip were then re-adjusted to bring in the data set of interest, which is you know the 13,000 points ...the whole... the river system, and the results of that analysis is provided here. So we are showing concentrations from the table of 0.5 ppb all the way up to 20 ppb, the probability of occurrence.

The probability of one PPB was up there at the 99.93 percentile, and that equates to really the equivalent of being equal to or exceeded .07 percent of the time. That's 7 out of 10,000 chance of occurring. If you look at the...our W.A.R.P. prediction of 0.68 that's a 0.2 % probability of occurring, and maximum in

the N.W.Q.A. data set of 5.82 was 2 in 100,000. So we feel that the probability analysis confirmed that we are getting high probability exposure values from, you know, out of the N.W.Q.A. data, and the W.A.R.P. monitoring.

In summary, from all of our surface water studies, with the same crop treated, the P.C.Y. is critically important for an accurate prediction of exposure for niche products like Carbofuran, and the weight of evidence of our analysis has really shown. Estimated drinking water concentrations in the subpart per billion level and more toward an upper end level of one part per billion. At this point Dr. Fawcett will take over and provide an overview of the ground water assessment.

DR. FAWCETT: When I was first contacted by FMC to see if I had interest in participating in a project to try to define the risk of Carbofuran reaching ground and surface water I was at first a little surprised by the concern. Because to my knowledge of the monitoring literature Carbofuran had been really a very rare detect, in either ground or surface water, especially in the major areas of its use. I was of course aware that back in the late 70's early 80's that Carbofuran was detected in wells on

Long Island New York, along with some other pesticides, where it had been used at relatively high rates on the sandy soils in potato production. And for that reason, use on Long Island was then prohibited on a label.

So there were some localities where detections had occurred, but there were other localities where detections were very rare. So it was an interesting discrepancy to try to understand and explain, but it's a very important discrepancy, because as you have seen, EPA used a perspective study conducted in Maryland to calculate their estimated drinking water concentrations for all localities and cropping systems. And that site in Maryland was chosen to try to replicate the Long Island conditions.

So why might we have more detections in some areas than others? Or maybe fewer detections today than in some older historical monitoring studies? One of the factors is the reduced use. We've seen how it's become a niche use product, used on less than one percent often of the acres.

So when we look at some of the older monitoring studies, maybe done in the 80's, it was used on at least ten times as many acres. So if we are going to use those older studies to interpret for today, we can of have a ten-fold safety margin there.

But also there are specific vulnerability factors. We really need to have all these together: Sandy soils, coarse soil, shallow groundwater, but also have acidic soils and acidic groundwater. We need all of those factors together to get that vulnerability. And we also need to keep in mind that there have been a number of previous label changes.

Some of it you have heard about already; that have reduced or prohibited use in vulnerable areas. Use was prohibited in Long Island, New York, in 1984. A groundwater advisory was added to the label in 1985, advising against use where soils were coarse and groundwater was shallow. And then there were some specific changes addressing the more vulnerable regions, due to soil type or groundwater depth.

Sequential treatments were not allowed on those vulnerable soils in 1997. So you could only apply the product once, not twice. And significantly, the potato rate was reduced from 6 pound per acre - which is probably what they were using on Long Island when they got into trouble - from 6 pound down to one pound per acre in those vulnerable soil areas. Again EPA's tier 2 assessment, they based it the perspective groundwater study in Maryland. And that site is very unique, again selected to try to mimic Long Island.

It has a sand soil texture, not a loamy sand or sandy loam, but a true sand with greater than 90% sand particles. This soil was very acidic, with a pH of less than 5.8 for all measurements, and often far below that. The ground water is also acidic, all measurements were less than 6 and many below that, and of course being a monitoring study, it had a relatively shallow well depth of 13 to 14 feet.

Why is pH important? pH is very important to Carbofuran persistence, and therefore the leaching potential. The longer it lasts in the soil, the greater the chance that it might move through the soil to reach wells, and once it reaches water, the lower the pH, the longer it will last and the greater the chance that it may show up in that well.

We have seen some earlier numbers, the half life depends upon the experimental conditions, but here is a study that looked at soil half life, at pH 7 the half life was 23 days, reducing the PH to 6.6 increased that persistence to 43 days. Similarly in water, at a pH of 9 Carbofuran has a half life of 12 hours. We don't want to mix Carbofuran in alkaline water in the spray tank, because it breaks down in the sprayer too quickly to get the activity. If we look at pH 7, the half life is 28 days and down to pH 5 it becomes

stable. So low pH's make Carbofuran more persistent, and more likely to reach ground water.

We began our analysis, and really we did it in 2 stages, we first concentrated on those green states, essentially the corn belt, the higher use areas for Carbofuran. Corn belt and 3 specific states in the Pacific Northwest where it is used on potatoes.

We then conducted a separate analysis essentially of all the states east of the Mississippi that we had not previously analyzed. This included areas that we assumed to be more vulnerable. Where we had more sandy soils and where that Maryland site of course is. But they were lower use areas. The first thing we did was to try to find all of the monitoring studies that we could find in the literature. And EPA did identify many of these areas and they summarized them in their document, but we were able to find some additional monitoring studies, and partly some large ones in the heart of the corn belt.

Those studies were done anywhere from 1983 to 2005, and an important source of data for us was that National Water Quality Assessment. And those studies were done anywhere from 1993 to about the present. So it gives us a little more recent data set, and a very high quality extensive study. Soil texture, we wanted

to identify those high sand soils and used the Statsco Database to get at that. Water pH, we got from either published studies, or surveys in states or databases or in some cases we used the N.W.Q.A. data set for water pH. Soil pH, rather than use a database, to try to eliminate the complication of non-agricultural soils, we contacted state soil specialists in each state, and got their professional opinion of the typical ranges of surface soil pH's as well as subsoil pH's.

Vulnerability, including aspects such as groundwater depth, we ended up using EPA's County Drastic Database, and I'll say a little bit about drastic in a minute. And we also tried to get Carbofuran use survey's to try to match the time periods that these monitoring studies were done. For many of the earliest studies we used state pesticide surveys, kind of the mid ranges, we used the mass of the National Agriculture Statistics service numbers, and for recent use we accessed FMC's sales figures.

Many of you may be familiar with or heard of Drastic before. It's a tool to measure the relative vulnerability of groundwater. I won't read through what all of what the acronym stands for, but you can see the many factors that go into that, into that calculation. When you apply Drastic you end up with a

score or a number. The higher the score, the more vulnerable that site. For example, Wicomico Maryland, that's the county in which the perspective study was done, the score for that county is 185.

Undoubtedly if you calculated a score for the study site, it would be a higher number, because it was selected for it's vulnerability. But the county average score for that county is 185. That's an important number, because we'll use that as a benchmark later.

To look at some other vulnerable areas, Suffolk County, New York on Long Island, the score for that county is 195. For comparison purposes, to look at some higher use areas to the west, just to see what the numbers would be. Cedar County, Iowa, that's where my home farm is, the score for that county is 137. Washington County, Mississippi, down in the Delta, the score for that county is 144. Polk County, Oregon, is out in the Willamette Valley, the score there was 122.

We chose to use Drastic as a tool, in a tiered approach to try to identify potentially vulnerable areas. And we use that 185 as a benchmark, that Wicomico County, Maryland. This map shows all the counties in the United States that had a score of 185 or more. And you can see that its almost all centered

over here on the eastern seaboard and down through Florida, with very few other counties scattered across the country.

We then took an overlaid Carbofuran use data on those high grassy scored counties to see if we had both vulnerability and use. This shows for 1992, the highest use is in red, but even there, that's 5 pounds per square mile, even there, low use compared to other pesticides. This shows use in 2005. What we did then, was by using this, even those we'll see in a minute; the detections of Carbofuran in that region have been very low in the N.W.Q.A. data since 1993. But to make sure that there was really no question about, worries about contamination. We recommended..the amended label has a number of geographical prohibitions. Florida, North and South Carolina, the DELMARVA Peninsula, are all prohibited from use. And those other scattered counties are addressed, as well set backs, which I think you heard about earlier.

Let's look at the monitoring results. We've got this divided into 2 sides, a left hand side of the slide are the major use areas, the kind of corn belt and potato states. On the right side and slide, are those states on the east of the Mississippi. Looking first on the left, there were 9,431 private, public and

monitoring wells in that universe of data. It's important that there were private wells, because EPA is rightly concerned, that if you for example simply look at safe drinking water monitoring data that you'll miss the private wells. There were many private wells in the surveys.

There were also a lot of monitoring wells. An important part of the N.W.Q.A. data set are shallow monitoring wells on the edge of agricultural fields. So we should have some of those worst case scenarios in the data set. Looking at those western wells, I think there were a total of 18 detects for a .19 % detection rate. So really very rarely detected. And whenever we talk about detection rates we need to consider detection limits. N.W.Q.A. has very low detection limits of .028 or .003, depending on the method used. And while there were a few studies in the 80's that had higher detection limits, most all the other studies had detection limits of about .5 or less.

Looking at the highest concentration found in those western states, that was one part per billion. Found a well in Iowa. So there were no wells that came anywhere close to approaching EPA's estimate of 17 part per billion for their corn scenario. That well in Iowa, I am very familiar with, because I made a

personal investigation back in the 80's. And it did have a commercial mixing, loading, disposal site very close to that well without any documented containment in those years. At least it was my opinion it was probably effected by that point source.

We shift to the right side of the slide, we contrast to the states to the east. About 7,000 wells in that data, and you can see the detection data was higher; 2.56 % detection rate. Important, if we look at the N.W.Q.A. data, and again that's 1993 onward. It was about half the detection rate, despite the very low detection limit, detections were lower in those more recent years. Maximum detection it that was 36.6 part per billion back in '85, in a Massachusetts well, we really don't have the details to say whether it was a point source or something else, but that was the highest number in the data set. But it's important to consider that most of the detections, in fact all of the detections above 1 part per billion occurred in the 1980's.

Before those label changes that reduced use or prohibited use in vulnerable areas. Since 1993, in that N.W.Q.A. data set there was only one N.W.Q.A. well that had a concentration above 1 part per billion, and that was 1.3 part per billion in a Connecticut well.

Just to give you an idea of where the monitoring is done, these are the N.W.Q.A. watersheds we don't report on in those far southwest states, this shows where all the N.W.Q.A. watersheds are. And here we have overlain the locations of those additional studies we've located. Often times they were just a few counties and states that were aimed at vulnerable areas, but you can see there in the heart of the corn belt they were statistically designed statewide surveys for Nebraska, Minnesota, Iowa and Illinois; an important use area. Let's look at where we have the N.W.Q.A. detects, because we have geo-referencing for all of those wells, we can show you where the detections were, and where the non-detects were.

These are the detections for Carbofuran in the N.W.Q.A. wells. This just shows detection remember all those except one were below one part per billion, and about 99 % of them were at a tenth of a part per billion or less, so usually very low concentrations. That shows you where the detections were. This shows you where the non-detects were. So you can see exactly where the monitoring was conducted. And I have here on the lower left, we show that the Carbofuran use map.

It's very important, because if you look this, this is kind of one of the higher of use. It

just matches very closely, this area of higher monitoring. Also in the Northwest we have monitoring going on where there is the highest level of use. Also important to note; here along the Eastern Seaboard, very intensive monitoring in those vulnerable areas. So the N.W.Q.A. gives us intensive monitoring both where Carbofuran is used and in the more vulnerable areas.

What are the factors that may explain the discrepancy of the more detections in the East? At least in those early years of monitoring in particular. Again, looking here on the left side of the slide we are looking at those more vulnerable eastern states. Sand texture was greater than 5% of the surface soils for 12 states. If we go over and look on the right for the corn belt and the Northwest, it was less than 5 % for all states except for Michigan and Nebraska. And talking to soil specialists, those sandy soils in Michigan and Nebraska were not real crop soils. Look at Drastic.

For the states to the east the Drastic scores above 185, the county scores range from 0 to 88 %, but there were 7 states that had greater than 10% of soils, or counties having a Drastic score of 185. To the west, there was only a single county in Minnesota that

had a Drastic score of 185 or more. Far, it's rare to find those vulnerable counties in those major use states. Water pH's, in the east, generally low, they were below 7. The mean pH for all the wells in the data we analyzed, below 7 for 14 states. In the west, they are above seven for all states, the mean pH.

In fact, there are only a few wells, single wells in Texas, that had a pH as low as that Maryland site. Soil pH's are a similar story, much lower in the East. In particular the sandy soils and humid areas, it's not uncommon to find low pH soils, often as low as 5.5, and in the subsoils as low as 4.5. It's kind of the opposite as you go west, the farther west you go, the higher the pH soils are. Often 6 to 7 for many corn belt states, 7 to 8 as you get to Nebraska, west. And in contrast with the East, subsoils tend to be higher in pH, because of the presence of calcareous porent materials or other reasons, so we have in the East, lower pH's, and in the West, higher pH's.

So from that monitoring analysis, we are confident that present use of Carbofuran results in a very low risk of groundwater contamination. And in fact in 99.9 percent of those N.W.Q.A. wells analyzed since 1993; 99.9 percent were equal to or less than .17 part per billion, so far below one part per billion.

But we wanted to carry the analysis farther, and look really at a more national scale. EPA agrees that Drastic is a useful tool to find vulnerable areas, but there may be other tools that are also concerned that the monitoring might have missed vulnerable sites. So Waterborne conducted a national Carbofuran leaching assessment, where they uses Prism, the Prism model to simulate all agricultural soils, the entire U.S., 64,000 soils. Assumed 30 years of consecutive use of Carbofuran, in that model, and to measure the leaching concentration at 5 meters below the soil's surface.

It was then loaded into an Aquifer model to predict concentrations of Carbofuran in shallow ground water. Both simulations were conducted either with or without the geographic and soil restrictions that you have heard about. And calculating maximum daily concentrations, 95th percentile, or 90th percentile for each of those runs. I am going to very briefly in the interest of time just show you a snap shot of the results of that nationwide analysis. Again, assuming Carbofuran was used on every acre in the United States. Again, this is the results from the amended label, that has those geographical and soil type restrictions. Across the top you have the spatial, less than 1 percent of acreage, less than 5 percent, and less than

10 percent of acreage.

Over on the left you have either the maximum concentration that was predicted, or the 95th percentile predicted. And you see that those are all low numbers, nearly all except for that one maximum value, less than a part per billion. To kind of put it in words for the non-statisticians like myself, if all eligible were treated at the one pound rate per acre for every year for 30 years, and all the acreage had a ground water depth of 5 meters, or about 15 feet, and of course many areas don't have that shallow ground water.

Then a concentration of .22 part per billion would be expected to be equal or exceeded 5 % of the time on less than 1 % of the acres. So it does confirm that the expected concentrations really are low. Less than the 1 part per billion that we have been talking about.

In conclusion, on the ground water, expect drinking water concentrations in ground water due to Carbofuran use are expected to be less than a part per billion. Or there is room in that risk cup for that amount. This is shown by the modeling in the National Prism Assessment, as well as that monitoring data. Ninety nine point nine percent of the almost 9,000

N.W.Q.A. wells since 1993 had a concentration of equal to or less than .17 part per billion.

We also believe that the potential for ground water contamination can be mitigated through labels changes, and being conservative to remove some of those worries about potential contamination. The amended label that went in has use...all the old prohibitions are still there...things like Long Island, the things you have heard about earlier.

But new prohibitions include all of Florida, all of North Carolina, all of South Carolina, and all the DELMARVA peninsula are prohibited from Carbofuran applications. For some of those few other scattered counties in other states, there is a well set back of feet 50 feet required in those specified counties. There is a new prohibit, a new label addition that prohibits the mixing and loading and disposal activities within 50 feet of a well, unless you have an impervious pad.

To address the surface water concerns for some of those counties you heard about, identified in Illinois, Louisiana, and New Mexico, and all of Texas and Pennsylvania, the label now calls for 66 foot buffers adjacent to streams. I'm sure where many of the panel members wonder where that 66 feet comes from.

It's of course to both to be protected and compatible with government farm programs. In order to get paid, farmer to be paid, to seed down those buffers with a conservation reserve program, they need to be at least 66 feet. On my farm, we have several miles of buffers, along all the streams and many of these buffers were already there, with help, with things like the conservation reserve program.

I want to end with some quick acknowledgments of some of the other scientists involved in these studies, particularly monitoring and modeling. And we have a few key questions like some of the other speakers have had, that really relate to what we have talked about here, I'll just leave them on the screen for a minute.

I want to turn it over now to Keith Solomon, and I know he'll be brief. I know he has a plane to catch, but I think he has 3 slides on aquatic toxicology, we have of course been dealing with the drinking water aspects.

DR. HEERINGA: Dr. Solomon, then we'll take questions.

DR. SOLOMON: Mr. Chairman, panel members, I just had actually 3 data slides, and 1 title slide, and it covers a large area. In terms of aquatic

risks, this was not a charge question to the SAP, and it was mentioned yesterday by EPA. There are 2 documents that are being provided to the panel that overview both the aquatic and the mammalian risks. And just to briefly cover the aquatic, we obtained toxicity values for aquatic organisms from the US EPA's ecotox data base.

We also used microcosm based, this is experimental ecosystem based no observed effect concentrations from Theo Broxworth in the Netherlands, and Bartoningen and then we looked and compared these two exposures, calculated by EPA in the IRED, also using the N.W.Q.A. data that has been discussed previously, although we did test a hypothesis that there were changes in the pre 2000 and the post 2000 data, and we also used the one part per billion maximum concentration that was talked about in the presentation just given. So this starts off with a quick species sensitivity distribution survey.

In the hollow points, the fish data the fish are less sensitive to Carbofuran that the arthropods and the solid points, and this just indicates the range of susceptibility to Carbofuran in these organisms. Now if you overlay on top of this the estimated concentrations from the IRED, you will see that fish

are still above the maximum concentration that they estimated, but obviously there is some overlap with the arthropod concentration.

However it you look at this in the context of the Brock microcosm studies, which really show the low observed adverse effect concentrations for microcosms, which integrate many different species and interactions between them. What you see is, this actually is very close to the lower limit of the concentrations estimated by EPA, and it still obviously exceeds some of the toxicity values for the arthropods.

The reason for this is that the LC 50 testing in the laboratory probably maximizes exposure which does not occur in the real world. If you then place on top of that the water concentration for the presentation you just heard, you will see that somewhat lower risks would be even less, lower from the Brock microcosm reviews. I took the N.W.Q.A. data. I can't show the individual data points, there are too many of them, and it ceases the system up. These are the regression lines, and you can see here that the intercepts that some of these values on the basis of some fairly high concentrations from places like Zonner Creek, that we talked about earlier, in excess of 99 to 99.9 percent, so a very small probability that these

very high concentrations will occur and that adverse, threshold adverse effects would be seen.

In terms of mammals, one slide. Mammals are less sensitive than birds. And I am going to rely on Dwayne Moore's modeling here. The mouse is the most sensitive of the mammals, from the IRED 2 mg per kg and the least sensitive mammal that I saw was the dog at 15. But in many instances these, in situations outside of misuse and baiting, there would be similar exposure reductions that we talked about in the avian risk assessment, and in all likelihood they would have a lower risk than for birds. And this I think is consistent with the incident data, which excludes misuse. If you look at the data, flowable uses are only a very few incidences associated with mammalian mortalities. There were more on the granular material, but of course that's no longer in use, so thank you very much Mr. Chairman.

DR. HEERINGA: Dr. Solomon, Dr Fawcett, Dr O'Neil. Questions from the panel? With regard to the presentations on water. Dr Sparling.

DR. SPARLING: Don Sparling for Southern Illinois University. With the, I'm not familiar with the Drastic score system. Why was 185 chosen? And how high do values go for Drastic?

DR. FAWCETT: One eighty five was chosen because it was the value that was associated with that Maryland prospective ground water monitoring study, and I think values generally ranged maybe up as high as 240. That would be like up in Broward County Maryland, I mean Florida is in that sort of ballpark. Maybe higher than that, 247, or something like that, it's a relative index in its approach to relative vulnerability. Mr Williams.

DR. HEERINGA: Other questions on the presentation on the ground water or flowing water? Okay, I want to thank you very much, again, for your concise clear presentation. We have final, Mr. Kleingartener, we have one more presentation left to go before, I think. Mr. We have one more presentation from FMC, just a wrap up that Dr. Cummings will do. We are going to finish out after Dr. Cummings' summary presentation. We are going to go to Mr. Kleingartner and Mr. Engel from, representing the National Sunflower Association, the sunflower growers. But let's continue with the final presentation from FMC.

DR. CUMMINGS: Thank you Dr. Heeringa. I only have about 3 or 4 slides, it shouldn't take much more than an hour and a half. So we should be in pretty good shape. I am pretty sure I

am not going to get questions, so... . Real briefly, I just wanted to summarize after, I was going to save my thanks for the end, but I think I do want to thank the chair as well as the entire panel for their patience, endurance, level of participation. Certainly their attention throughout the... it's been a long day, and we certainly appreciate the registrant having the opportunity to present our scientific position to the panel, and for their consideration.

Just real quickly, what I would like to do is just summarize from a risk perspective what you've heard in these scientific presentations today. And hopefully what you've heard is that a reasonable set of assumptions have been presented, scientifically justified, and they support the conclusion that from an F.Q.P.A. risk perspective, all of the crops that F.M.S. is proposing to move forward with, that is the import tolerances, the phase out crops, which will be phased out over the next 3 to 4 years, as well as the 5 critically important crops, do meet the F.T.P.A. standard, and fit within the risk cup. Now just to reiterate this one slide very quickly, you saw it earlier, it's not quite as neat and clean, I think it is actually shown up on the side over here in a little bit different form, but essentially if the F.T.P.A.

safety factor is reduced to 1 - as is our position - as well as reducing the inner species safety factor from, well either maintaining it at 10, or reducing it to 3, and maintaining the intra species safety factor.

There is, the food exposures do fit within the risk cup and leave ample room for water contributions. Basically to conclude there, is that also we hope you've heard in the water segment of the discussions is that there really is negligible contribution to surface, from surface and ground water to the risk cup.

Generally low to minimal avian risk. There have been mitigation measures to alleviate any concerns of avian risks, of higher risk, and that there are acceptable margins of safety for workers. And in addition, what you have heard along these critical and important uses is that the benefits essentially do outweigh the risks associated with the use of the product. And I am not going to go through this, but just, it's in your packet and these are the, just kind of a re-cap of the scientific questions that the registrant would feel that the SAP. should consider, if they feel appropriate. So I'll go through those quickly. Finally, I think to reiterate my comments, earlier today, I guess much earlier today now, we do

feel based on sound science that the science does support continued registration of Carbofuran in the United States, based on the amended label. I would like to thank the panel again for their attention.

DR. HEERINGA: Thank you Dr. Cummings. Questions for Dr. Cummings in the wrap up from the panel members? Okay, Dr. Cummings and your team, thank you very much for your all of your presentations; and panel members, thank you for your questions and your patience. In case anybody is wondering, this is not the latest a science advisory panel has ever gone. I understand that genetically modified corn went on almost until midnight on one of it's days. Charlene was there, so we will . . . no pizzas.

Okay, returning to the program, we are going to have 2 public commenters this evening, to do them the favor of allowing them to get out. The first Mr. Larry Kleingartner, who is representing the National Sunflower Association, Mr Kleingartner.

MR. KLEINGARTNER: Thank you, Mr. Chairman and members of the committee, for accommodating us and I appreciate your work on this subject. We just want to give you a little background. You have heard obviously lots of laboratory kinds of

things, and we want to take you to the actual production field and talk about one crop that would be impacted in the absence of Carbofuran. Just some quick sunflower basics. Sunflower is really a fairly minor crop in the United States, several million acres, but the product is very important in terms of demand, in terms of nutrition.

It has, it is a naturally stable oil; sunflower oil is. So it doesn't have to go through the hydrogenation process, which results in trans-fatty acids. So the potatochip companies in the United States, a lot of snack food companies see this oil as a very, very primary oil in the production of their products. And it is also very low in saturated fats. So it really is a preferred oil. We also produce confection sunflower seeds, and if you are a baseball fan, you'll notice that a number of baseball players love to chew and spit sunflowers in absence of chewing tobacco.

So I'm hitting all the health events here. And it's also very high in folic acid and vitamin E, and we can go on and on, 'cause you are going to hear this from the potato people tomorrow. Here are just a few of the products you know that, Frito Lay has really become a major, major customer, they are the

largest snack food company in the U.S., and they switched a majority of their products to sunflower oil, to eliminate trans, and to lower saturates. I found a Jim Beam up there.

Even though it's more Miller time right now, for you Jim Beam people, there are sunflower seeds that are soaked in Jim Beam, and you can get a little, you can get just a little kick from that as well. I didn't bring any samples, I didn't think I could get them through the process out front. But let me get on to serious stuff here.

The sunflower plant is a native species plant in North America, and with that we've got some fairly significant and native insects, and they've been here for centuries, and once we throw up a 200 acre sunflower field with nice big juicy heads and stalks these native insects just have an absolute field day, like kids in a candy shop. Because we are a native species crop, the G.M.O., the Genetically Modified Option is not possible for us at this point in time in the regulatory phase, because of the potential of outflow of the genes to the wild species. So, as far as "quick fixes" for some of these production issues, the G.M.O. is not an option. This is just kind of a "look-see" of where the production is at.

Let me get my laser here, this is where we really have more of our insect problems, related to the insect that we are talking about here, that we need Carbofuran for. It's really in the Colorado, Kansas area, and you see it's a fairly concentrated production region. And again, it's a native insect that has been with us, and this is it, the Adult Stem Weevil, it's a very difficult insect to scout for, and I have a producer, Mr. Unruh, who is sitting beside me and he'll talk about that in just a minute.

It's a very cyclical population, as most insects are, and Carbofuran really is the only effective control. We're not using a lot of this problem, I mean a lot of this product. But in this particular area of the United States this insect is rampant, and is there every year. And to produce this crop successfully this is really the only product we can use. In this area of Eastern Colorado, Western Kansas, there is about $ 200,000,000 worth of infrastructure in place for processing this crop, so it is a center of production.

The Stem Weevil basically impacts the stem, it lays eggs, the larvae burrow into the stem, they float up and down that stem all season long. We've counted as many as 100 larvae in a stem, the stem is

weakened when there is that kind of pressure. You've got a heavy head on the top side, with a weak stem on the bottom side. You get a little breeze, which we have quite a bit of, in Eastern Colorado and Kansas, and you can see what happens when in that bottom photo.

They just basically tip over at the base. We also have some secondary diseases that the Stem Weevil is a vector for, and in essence, the hole in the stem creates the pathway for these pathogens. And that's the Charcoal Stem rot, and the Phoma Black Stem. And those are fairly significant diseases when we get this kind of pressure. Our response, we have been testing genetic material in Western Kansas for the last 5 years. When I say "we", it's a combination of state universities, and the U.S.D.A.'s Agricultural Research Service.

We have found good segregation in populations of wild species, and other you know, further refined stocks of genetics. We have recently as an organization, funded a poll stock, to take this research and move it to the next level and try to get this resistant material into hybrids as soon as possible. We look at that as a 6 year process before we really get into commercialization, so we need this lead time. And as you can well recognize, insect

resistant research is a fairly high risk kind of research.

In summary, Furodan is an important product for the production of sunflowers in this key region of Eastern Colorado, and Western Kansas. We don't have any alternatives. I'm not aware of any pesticide alternatives in the pipeline. We are working on hybrid resistance, and Furodan really becomes an important product for us with this kind of demand that we have in place.

We really can't afford to lose any acreage. Again, our demand is so strong we are importing sunflower oil to make up for the lack of domestic production, so an insect driving production out of this country would certainly impact domestic users, and certainly producers as well. So with that Mr. Chairman I will give the chair to Bruce, and we'll be happy to answer your questions.

DR. HEERINGA: Thank you very much Mr. Kleingartner. Before we turn to Mr. Unruh, I will ask if there are any questions from the panel. Yes, Dr. Hattis.

DR. HATTIS: What is the basis for your assessment that it is a unique product, that other pesticides, either Carbonates or phosphates, or from

other insect classes would not do the job?

MR. KLEINGARTNER: Yeah, the uniqueness of the product is that it translocates into the stem, and so the larvae then, as they are chewing the material, die. Other insecticides would all be contact insecticides to kill the adult, and the adult is laying eggs over a significant, I mean a fairly long period of time. And that's what makes it unique.

DR. HEERINGA: Dr. Lu.

DR. LU: Quick question, this is sort of a personal education question. So how do sunflower farmers apply pesticides like Carbofuran to such an enormous land?

MR. KLEINGARTNER: If I could let Mr. Unruh answer that question, because he actually does the, does the-

DR. LU: Okay, second question is, has the trade group ever measured say, Carbofuran residue in sunflower seed oil?

MR. KLEINGARTNER: Yes, all of that is in place since early in the process of the plant development. To my knowledge residue is not an issue at all. If it were, we would be out of, we would not be using this product.

DR. CARLSON: Mr. Chairman.

DR. HEERINGA: I have to stay with, Mr. Carlson, I have to stay with, if you have some clarification that can be passed with the other public speakers, I have to stay with this at this point. Bruce Unruh, I guess we have answered the question about application, and-

MR. UNRUH: I'll touch on that in mine in a little bit. We're pretty much over that. My name is Bruce Unruh, and I farm at Burnett Colorado. That's East/Central Colorado, about 14 miles from the Kansas border, and I raise wheat, corn and sunflowers. Our average rainfall is 17 inches, so water to us is a precious commodity. I use Furodan on the sunflowers for Stem Weevil and on corn for Root Worm control.

Without the use, sunflowers I have had up to a 30% loss. Because of the Stem Weevil, I have seen neighbors that have had losses even greater than that. When this thing hits and the wind blows, we have had straight line winds before harvest at 60 miles per hour and it blows everything over.

If Furodan were banned I would no longer be able to grow sunflowers, because Furodan is the only labeled product right now on the market for use with Stem Weevils. So It's like, if we can't put that on we would be off label and where I grow confectionary

flowers, they are very critical with the residue, because you eat them, and so there are only certain periods. As far as putting it on, I use a half pound of actual ingredient at planting with the seeds, so it is put approximately 2 inches in the ground and covered up.

The other stage, if it doesn't go on then, would be at approximately a B7, 8 stage, which would be a little bit under knee high, and it be over the top, and still at the same half pound of active ingredient, so it's not a heavy rate we're using, just enough to knock this thing down, and keep it held down.

On my farm, like I say, 2,200 pound flowers, 248 acres, 30 cents a pound, 30% loss, would be $ 47,000, which you only stand that about one or two years, and then you are looking for another occupation. On the next page is pictures that Larry showed, and he talked about the Stem Weevil bores into the stalk. When the wind blows at harvest that's why it falls over. The other thing is to go down low, we go down low with like snouts on the combine. As you start picking things up, you pick up a lot more stalks. You get docked at the elevator, they don't want all the trash, so you can't separate it with the combine. Like Larry said, when you've got a heavy and a short stalk

the stalk sticks up, and you get the stalk for free. Because of the increased loss of sunflower heads there is also another problem that develops, it's volunteer sunflowers the next year, and if hybrid sunflowers get tough to grow, volunteers will grow fantastically, and they'll come up 2 or 3 times a year, which causes us another chemical operation, plus a loss of moisture the next year.

So, it kind of, as the ball rolls, you start creating more problems because of this. On the next page there it talks about Kansas State University's. . . what their estimated cost of raising flowers is, and where I arrived at my numbers. For lack of time I won't go through that.

Basically without this, I am looking at a $96, at least, loss per acre. So why am I going to continue to raise the crop? With the direct cost of losing Furodan would be over 52,000 on the total acres, the total cost to operate my farm would be much greater. More importantly, sunflowers are an integral part of my crop rotation, so it's not like I put Furodan on every acre every year. This would be like a 3 or 4 year, so it gives time for the soil and everything to digest it, and it wouldn't be like the water issue, or anything of that nature. Integrated

pest management; I have observed neighbors who have been in flowers for 4 years, not used Furodan and have had some major losses.

Last year I watched a neighbor lose, I know he was at 30%, I didn't go out and look much closer, but you could tell it was bad. Later planting dates, where we're at, doesn't seem to help. Also we start losing yield at that stage of the game. Other chemicals, like I say, there is nothing else labeled. So there is no other product. You grow them and hope for the best, which that doesn't always work.

The lower annual rain fall in my area limits the alternate crops that we can go to, so it takes my rotation and changes that picture completely. Like I say, without Furodan, I don't think I'll be able to grow sunflowers, so I just appreciate your studying into it, looking at everything with a very open mind, and I just thank you for your time and effort.

DR. HEERINGA: Thank you very much, Mr. Unruh. Questions from the panel? Yes, Dr. Kehrer.

DR. KEHRER: Jim Kehrer. Mr. Kleingartner said that the weevil problem was cyclical, but it sounds like you treat the sunflowers every year with Furodan, is that true?

MR. UNRUH: When I grow sunflowers I

treat them every year, because to scout them, when you walk out there in that period they drop to the ground, and because of the color they look like the ground. All the consultants that I know will not even scout for them. They just say at a certain stage you have just got to put it on, or you are going to lose them, so they come up every year.

MR. KLEINGARTNER: If I could clarify, they are cyclical in other parts of the country, but in that region where Mr. Unruh lives they are consistent, yeah. But up in the Dakotas and Minnesota we may see them every 6 years or so, but not to the volume that we see consistently in this area of Eastern Colorado, Western Kansas, and that's why we are doing all the resistence testing there. Because we have a continuous cycle or a continuous population of the insect.

DR. LU: So you forgot to tell us how you apply the Carbofuran on the sunflowers.

MR. UNRUH: I apply it at planting, at the half pound of active ingredient with the seed, with the starter fertilizer at the time. So it is put in, in the furrow. The other time is approximately like a B7, B8, about knee high, and then we come over the top of the ground grade.

DR. LU: So it's like an aerial spray,

or-

MR. UNRUH: No, it's for the ground grade. Like just a close sprayer.

DR. LU: Okay.

DR. HEERINGA: Dr. Sparling.

DR. SPARLING: Don Sparling, Southern Illinois University. I know the sample says there is only one farm, but after application of Carbofuran, have you ever found dead birds in your sunflowers?

MR. UNRUH: I have not found dead birds around Furodan since granules have been gone.

DR. SPARLING: Have you looked?

MR. UNRUH: Yes, yes, I walked the fields and looked for other pests because a little bit after this we are going to come into head moth, and other pests start showing up. And these are on sprinklers, which we have to go out and check everyday, so I have driven around and walked and have not found any birds.

MR. KLEINGARTNER: Mr. Chairman, if I might, on the back of my presentation there is a copy of a news release from the Department of Justice, which deals with the issue of the Colorado producer who was found to mis-apply. If you notice in the second paragraph, the second sentence, he relates to the mis-

application of the chemical. To our knowledge in the sunflower industry, this is only time we have heard of any bird kill related to this product.

DR. HEERINGA: Since I have opened it up for you, Dr Carlson, did you have something related to the detection of sunflower oil?

DR. CARLSON: Yes. Don Carlson, with FMC Corporation. There was a question raised relative to, would there be residues in sunflower oil? Virtually all oils, whether they come from sunflower or any other oil seed crops go through a process for processing the oil. In the stage going from raw oil to refined oil it is usually treated with a very alkaline treatment, and in that step as a result of a the highly alkaline treatment, all residues of Carbofuran, either Carbofuran or 3 Hydroxy Carbofuran would be completely destroyed. And the EPA has verified that, and agreed to that conclusion. Thank you.

DR. HEERINGA: Thank you Dr. Carlson. You answered my question about why these bugs don't show up in the Dakotas. Because that's where my mother's family is from.

MR. UNRUH: Fortunately we have different bugs there. But we have alternatives to Furodan.

DR. HEERINGA: But the wind never blows.

MR. UNRUH: The wind never blows.

DR. HEERINGA: Okay, with that, I think I would like to draw today's proceedings to a close. Before I do close, I want to thank everybody for their patience today. We will resume first thing tomorrow morning at 8:30 with a continuation of the public speakers who have registered to speak. Again, if you are in the audience and have not had an opportunity to speak but wish to speak, please see Dr. Matten, to register for a 5 minute presentation, and Dr. Matten has a few closing comments before we break.

DR. MATTEN: Right, I think it was this morning still, the health effects divisions personnel, they gave a number of clarification slides in the morning in they have made printouts of those slides, plus they answered Dr. MacDonald, maybe, about the sourcing of various materials, data in the matrix table and so that is also provided. And then after that meet next door.

DR. HEERINGA: Panel members if we can meet briefly in the break out room, thank you everybody for your participation today. See you tomorrow.

(WHEREUPON, the session was concluded at 6:33 p.m.

CAPTION

The foregoing matter was taken on the date, and at the time and place set out on the Title page hereof.

It was requested that the matter be taken by the reporter and that the same be reduced to typewritten form.

Further, as relates to depositions, it was agreed by and between counsel and the parties that the reading and signing of the transcript, be and the same is hereby waived.

CERTIFICATE OF REPORTER

COMMONWEALTH OF VIRGINIA

AT LARGE:

I do hereby certify that the witness in the foregoing transcript was taken on the date, and at the time and place set out on the Title page hereof by me after first being duly sworn to testify the truth, the whole truth, and nothing but the truth; and that the said matter was recorded stenographically and mechanically by me and then reduced to typewritten form under my direction, and constitutes a true record of the transcript as taken, all to the best of my skill and ability.

I further certify that the inspection, reading and signing of said deposition were waived by counsel for the respective parties and by the witness.

I certify that I am not a relative or employee of either counsel, and that I am in no way interested financially, directly or indirectly, in this action.

CHARLES DAVID HOFFMAN, COURT REPORTER / NOTARY

SUBMITTED ON FEBRUARY 6, 2008

C

D

F

G

I

J

S

V

W

Z