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Reported by: Frances M. Freeman

C O N T E N T S

DR. PORTIER: Good morning. I want to welcome you to the FIFRA Science Advisory Panel for I guess today is Thursday, August 29th, on Corn Rootworm Plant-Incorporated Protectant Non-Target Insect and Insect Resistant Management Issues.

Today we'll be finishing up our discussion on insect resistant management issues. I'm Chris Portier, I'll be chairing the session today. I want to begin today by reintroducing the panel members, have them state their name affiliation and a brief background of what their research is and this morning we'll start with Dr. Hellmich.

DR. HELLMICH: I'm Rick Hellmich, I'm from the USDA/ARS, Ames, Iowa. I'm a Insect Ecologist specializing in insect resistant management and non-target issue requests Bt corn.

DR. FEDERICI: I'm Brian Frederici from the University of California at Riverside, Department of Entomology. I am an Insect Pathologist; I work on the basic molecular biology

and genetic engineering and bacterial insecticides.

DR. GOULD: I'm Fred Gould, North Carolina State University, I work in ecological genetics of insect adaptation to control measures and have worked on resistance management with Bt crops for a number of years.

DR. WEISS: I'm Mike Weiss, University of Idaho,

Integrated Pest Management in corn systems.

DR. ANDOW: Dave Andow, University of Minnesota, Department of Entomology; I'm an Ecologist and I have focussed a lot on to the ecology of insects and corn. I have been doing work in insect resistance management.

DR. CAPRIO: My name is Mike Caprio. I'm from the Department of Entomology at Mississippi State University. I am a Population Geneticist. I have focussed on resistance management to conventional and Bt products.

DR. HUBBARD: USDA/ARS in Columbia, Missouri. I have been working with corn rootworm

since 1986. And my research projects in Columbia, Missouri include native host plant resistance, resistance management and collecting biological base or data on corn rootworm to fit the needs of the models for resistance management.

DR. NEAL: I'm Jonathan Neal, I'm an Insecticide Toxicologist at Purdue University. I do research on rotation resistant corn rootworm.

DR. WHALON: I'm Mark Whalon, Michigan State University. I consider myself an Applied Insect Pathologist. I have worked in insect resistance management for my career.

DR. ROBERTS: I'm Steve Roberts, I'm a Professor and Toxicologist at the University of Florida, and Director of the Center for Environmental and Human Toxicology there.

DR. THRALL: Good morning, I'm Mary Anna Thrall. I'm a Professor of Veterinary Pathology at Colorado State University.

DR. PORTIER: I'm Chris Portier, I'm Director of the Environmental Toxicology Program at the National Institute of Environmental Health

Sciences, and I manage the US National Toxicology Program and my area of expertise is in statistics and risk assessment.

I would like to welcome you all here this morning. I know this takes a lot of time out of your busy lives to address these issues, but I think they are very important issues. Before we start with the panel discussion our Designated Federal Official, Mr. Paul Lewis, has some administrative details for us.

DR. LEWIS: Thank you Dr. Portier, again I would like to thank Dr. Portier for serving as our Chair in this meeting during the course of this week and for the members of the panel that have spent a considerable amount of time preparing for discussion we had yesterday and that will be occurring today.

Just as a manner of reminder again this FIFRA Scientific Advisory Panel is a Federal Advisory Committee such that we'll be following requirement for the Federal Advisory Committee Act we have a docket where all materials available for

this meeting are available for public inspection. This is an open meeting.

In addition, we'll be writing a report that serves as meeting minutes that summarizes the panel's recommendations and analysis for the agency. The report should be available in about four to six weeks.

In terms of today's agenda, if you notice on the agenda, we were planning to end around early afternoon. Again, the agenda times are approximates. We have a whole day allocated for discussion and we'll use the time accordingly depending on what time we complete our discussions today. Thank you, Dr. Portier?

DR. PORTIER: Thank you, Mr. Lewis.

Dr. Andersen, do you have any comments and would you also introduce your panel this morning?

DR. ANDERSEN: I would be glad to, thank you. I think, unless there are any question that are remaining from before issues, I think we have resolved all of them. I don't think there are any

overnight question that the panel has posed to us that we need to bring back. If I'm wrong let me know.

Again, we will thank you for spending, for some of you, the third day and for others just the second. We recognize that this is a lot of work, not only in advance of the meeting, during the meeting, but also after the meeting. We all certainly looking forward to your report and what you will be talking about today.

I'm delighted to introduce the people who will be working today on the issue of insect resistance management continuing on with the discussion from yesterday. To my immediate left is Robyn Rose, then Dr. Sharlene Matten, Allen Reynolds, and then Phil Hutton, and these are all members of the Biopesticides and Pollution Prevention Division.

And amongst us we will handle the electronics for this morning, so the questions can be up on the screen.

Thank you.

DR. PORTIER: Thank you Ms. Rose do you have any issues from yesterday's presentations or discussions?

MS. ROSE: No, I do not unless there is any questions for our staff.

DR. PORTIER: Barring that then, yesterday we ended our discussion by finishing question two and we were getting ready to begin question three which deals with models. If we can have the question read to the panel?

MS. ROSE: There are four parts to question three on models. Part A, the panel is asked to comments on the product duration or longevity of corn rootworm susceptibility considered in corn rootworm IRM models.

DR. PORTIER: Dr. Caprio, you are the lead discussant on this issue, but overnight we had a table prepared for us. I'm going to leave it to your judgment whether we should look at the table and the assumptions on the model or hold that for later.

DR. CAPRIO: I would like to see the

table, I guess.

Paul, is this the one I did?

DR. LEWIS: This is a table that is titled from Fred Gould.

DR. GOULD: I don't know if we need to discuss that right away.

DR. CAPRIO: I don't know what to say --

DR. PORTIER: That's fine, then let's go straight to this question.

DR. CAPRIO: -- to this question I think there is a wide variety of assumptions in the different models concerning dispersal rates and when it occurs. But we're dealing -- when you deal with a high dose, a lot of these assumptions are very critical. When we're dealing with moderate dose perhaps there is a little leeway if we think back to next doors's figures. As Fred pointed out, it is a relative flatness. There is still a lot of difference depending on how much refuge you put out there.

I'm not exactly sure what they want from this question. I guess the simplest answer is to

say that most of the models, if you take away the extreme assumptions, are in the range of 10 to 20 years.

Is that what you are looking for with this question, or do you want to clarify the question a little more?

DR. PORTIER: Ms. Rose.

MS. ROSE: To some degree, we're asking when developing a model, what is an acceptable duration that we should also be looking at is 10 years enough, is 20 years enough? .

DR. CAPRIO: In a way, that's what I look to you guys to tell us. That's really, from my standpoint, a policy question rather than a science question.

DR. PORTIER: Dr. Andow:

DR. ANDOW: Do I guess in terms of duration, here is what I would say, that all of the models that we have in front of us, and virtually any model they can think of, would give a product duration of at least three years.

The only case in which I can imagine

that would be faster than that is if you had a very, very, high dose type event that was adopted over 100 percent of the area, so that there was no refuge. And then you might get failure in less than three years.

But if the bar is just getting over three years, there is virtually very few scenarios in which you can imagine that it wouldn't last at least three years. So that's one point.

The second point, then, would be if you are looking, say, at 15 years with these low dose products, then there are certainly cases where it wouldn't go 15 years. And that's even some of those, one of those cases is identified in the interim IRM plan from the registrant.

But in many cases, it is going to hover around 15 to 20, 25 years.

In order to get higher, substantially higher, than that in the orders of 50 years there are some models that predict that under some broad conditions and other models predicted under relatively narrow conditions.

I think all of the models would suggest that increasing the refuge size would give you quite a bit more once you get -- if you are looking at refuge changes between 10 to 25 percent, you are not going to see much difference. Once you get around up in the 50 percent range, then you start to see substantial delays.

I think -- I'm pretty sure that all the models are suggesting that.

MS. ROSE: Could I ask for one clarification?

When you mentioned three years was that with a 20 percent refuge, or no refuge, or when you stated three years what was that based on?

DR. ANDOW: I was sort of saying, even under the high dose case with no refuge, that's about the only case in which are you going to find it happening within three years under the models.

So I guess what I was saying is there is virtually -- that virtually any case will get you three years. Doing nothing will get you three years. So it's a fairly low bar to get over.

DR. PORTIER: Other comments by the panel? Dr. Whalon?

DR. WHALON: Thank you. I would suggest a couple things. First of all, I concur with the comments earlier about the issue of how long is a policy issue and EPA should provide guidance there.

I would, maybe, help EPA in the process there by saying that there are several things that are assumed in the process of developing an IRM for a new transgenic corn plant and that is that there is a precedent that exists for pest resistance management plans for other registrants in the past in transgenic plants. Also, in this case, because we don't have a high dose situation, we're introduced or faced with actually a new, novel challenge. So I would back up and ask a more fundamental question, and that is is a refuge necessary?

I think the panel, I can't speak for the panel, but from my perspective, I believe it is. We believe that there is selection, or there is

evidence of selection, on the first instar though at probably low levels, low to moderate levels.

And given that, then, a refuge even given the current state of art of modeling and what we don't know in the field seems to be the prudent or the, following the principle of conservation, the appropriate thing for the agency to do.

Once that is established, then the issue of how long becomes -- comes into view and so far we have heard a lot of talk about 7 to 15 year horizons.

My question there is, why not a more sustainable strategy for these technologies a 30 to 50 year horizon? Why are we dictated by conventional insecticide patent horizon when these technologies have grower license agreements that would presumably perpetuate the technology further than a patent horizon?

So that historical paradigm may not be applicable here and that may be worth some discussion on the part of the panel to the agency.

DR. PORTIER: Dr. Gould.

DR. GOULD: I would like to get back to the models and the assumptions. I agree with what Mike and David said about most models having those time horizons, but we are dealing with a new situation with a beetle novel toxin. I think, Chris pointed out earlier, that we're always talking about in the models all the assumptions are ten to the minus three or ten to the minus four as initial gene frequencies.

Yesterday, Bruce brought up the point, can we look at the survivors and see if we have changed their resistance level? Quantitative genetic variation can, as opposed to what was said yesterday, be selected very rapidly if there is enough additive genetic variance.

I want to at least say, if you are doing a risk assessment, you have to recognize that all the other work we have done is on this high dose stuff where we had data on initial gene frequencies at least in a couple of Lepidoptera.

Here we're starting with a new ball game.

If you are doing risk assessment, if you want to look at potential worst case scenarios, we haven't gotten science information to give us the information about that. All the models are making a certain assumption.

Those are pretty conservative on the side of seeing slower resistance development. I'm not saying that they are wrong; they are probably right. But if you want guidance on risk assessment the models are making that assumption.

DR. PORTIER: Any other comments on this question? Dr. Caprio.

DR. CAPRIO: Just to follow up on what David said about the three year time horizon.

I don't think anybody considers resistance a threat. The question is really how much do you cost during that time frame in terms of changing resistance allele frequencies or loss of susceptibility and so on.

It is more a question of potential damage that you do, rather than out right resistance, during that time period. So I think

it is wrong to suggest it is not a problem, because we don't see the potential for resistance evolving in these three years. That's not the right question to be asking.

DR. PORTIER: Any other comments from the panel?

Dr. Andersen, you have a questioning look. I just have a clarification I would like to make so that the panel is understood.

The agency has not set policy, I do believe, it is policy, but the agency has not set a policy of what actual absolute years to resistance that we are looking at. We are certainly doing it case by case considering all of the factors. We have not set the bright line that we might say of some of the places where we have with other types of risk assessments.

DR. PORTIER: Dr. Whalon.

DR. WHALON: Personally, I think that's a prudent view given the state of the science.

DR. PORTIER: Okay.

So if I understand what we have talked

about here, that in terms of what would be predicted for longevity and duration of product utility, we're probably looking at something in the ten to even, maybe, 25 ranges. Our best guess from the panel, although again, because of the nature of the assumptions, we're not absolutely certain that this is more in the research realm currently rather, really in the more routine use for regulatory work. And that's because of the low dose effect.

We just haven't had enough experience with that. And in terms of the comment about what would be an acceptable number of years, I think the panel is agreeing that for this type of product, the more sustainable it is, the better it would be.

And I think that's uniform across the panel. I don't see anyone disagreeing.

DR. PORTIER: Dr. Andow.

DR. ANDOW: Not with that last point, but elaborate a little bit on your first point of summary.

I think that the exception that we identified were a case that doesn't hold here, the high dose case. And then Dr. Gould identified the case where perhaps there is already substantial resistance in natural populations.

The experiment that Bruce was talking about earlier, that Lance Meinke was doing, could help resolve that even before a plan could be -- a sound plan could be developed.

DR. PORTIER: Noted. Okay, should we go onto question B?

MS. ROSE: Question B reads considering EPA's evaluation of the three models addressed in the Monsanto submission, discuss the applicability of each of the models for assessing the likelihood of corn rootworm developing resistance to Cry 3Bb1.

DR. PORTIER: Dr. Andow, why don't you go first this time.

DR. ANDOW: I just wanted to consult with the lead discussant.

DR. PORTIER: Dr. Caprio can go first.

I'm just trying to be democratic.

DR. CAPRIO: It is hard to summarize all these. I guess back to what I said yesterday, there is a wide variety of assumptions about dispersal and when it occurs.

Various assumptions about dominance and some of those play a large role, particularly in Dave Onstad's model and the Monsanto use of the web-based model.

And I think they present a wide variety of potential scenarios. The ultimate result is that, you know, we're still talking something in this 10 to 20 year or 25 year time frame despite all those different assumptions.

The only one comment that I would make is about the Monsanto model, which assumed complete dominance, so their heterozygotes survived at a rate comparable to resistant, fully resistant individuals. And the result that that gives you is that there is very little impact of refuge.

And I would just say that that is not a

typical case that you would find from the other models where dominance is not -- complete dominance is not assumed. I would argue that even in this moderate dose, there is a strong case to be made for a refuge, a sizeable refuge.

I think Dave you mentioned earlier that the curve on this goes up as one -- goes beyond 20 percent refuge, as one approaches 50 percent or greater. I'm not sure if that is an adequate answer.

DR. PORTIER: Dr. Andow.

DR. ANDOW: I guess maybe I could get clarification from EPA. Are you want to go have a very detailed discussion of the -- this model assumes this, this and this, and this models assumes this, this, and this.

MS. ROSE: Yes. And are these assumptions are appropriate for this product and insect pest?

DR. PORTIER: And potentially taking it to the more general case of: are these models, would you argue these models are supported for the

case of low dose products in general or is there further development that needs to be made?

Since they were developed for high dose, do they really transfer to low dose case or is there additional research to be done? Would that be part of it as well?

MS. ROSE: Yes.

DR. WHALON: Point of clarification.

DR. PORTIER: Dr. Whalen.

DR. WHALON: I'm wondering in this context, then, if there is a presupposition in an interim registration situation that there would be responsibility on the registrant to actually develop the tools necessary to assess whether or not refuge a refuge is working.

DR. ANDERSEN: Those are decisions that get made partly based upon the advice we have.

Here, you might want to look at what we have done before as an idea of what we have at least considered in the past models where models became more and more important as one of the tools we used in looking at resistance management plans

for the lepidopteran products for corn and cotton.

So we have asked actually of the Scientific Advisory Panel in the past how important models are and they have told us these are one of the important tools in looking at.

And that's why we consider it important to say how robust are the models that we have at hand? Are these ones that we think ought to really be further developed?

Should we start over, find another model or is it is this really useful? Then, how the agency goes about deciding what to we might ask the companies to do, or other ways to get that information we have to make those decisions.

But I think unless you disagreeing, and I don't think you are, I say a few panels in the past have told us models are good tools. Given that, what are the kinds of thinks things we should have in this.

I might say I know we have broken this into four sections but as you look at it, question

C actually does lay out some various parameters of models that we thought were especially important.

They may not be the only ones, but maybe you can advise us. Again, almost answering the two questions at once.

DR. WHALON: May I rejoin on that, just to say that I concur in this situation, I think, that given conflicting information from the field and the state of the science that models are essentially all we have.

DR. PORTIER: So, in order to sort of keep us focused, might I suggest that we discuss in part B, then, the actual mathematical constructs themselves. The assumptions that are made in developing the models and for C, we go specifically to the parameters that are entry in to the models and the quality of those parameters in the given case.

Dr. Andow.

DR. ANDOW: To talk about all the models, generally, all the models generally are discreet timed models which seems appropriate in

this case, meaning that each generation is handled separately and then the models are updated.

In terms of another major distinction among models is stochasticity or deterministic models.

The store model is a stochastic model and the other ones, I believe, are not stochastic.

Now, in terms of how stochasticity is built into the store model, I have to say I don't know. I'm not sure if this is the same model as the one that I have seen before.

But the other ones that Nick has done, and maybe Nick can comment on this if I'm correct, have introduced stochasticity primarily in the vital parameters of the vital demographic parameters as in births and deaths.

Is that true in this case also?

DR. PORTIER: Dr. Storer.

DR. ANDOW: If it is a no, I would like an elaboration as to where it is.

DR. STORER: Just for clarification --

DR. PORTIER: Please, introduce

yourself.

DR. STORER: Nick Storer, I commented yesterday.

DR. PORTIER: And you are from?

DR. STORER: From Dow AgroSciences, I'm sorry.

DR. PORTIER: Thank you.

DR. STORER: The model you have seen previously has less stochasticity than is in this rootworm model. Elementary stochasticium in nearly all the processes affecting the genetics and end population processes.

DR. ANDOW: In particular, in terms of population variability, is this stochasticity handled through the vital parameters and others through the demographic parameters that are built into the model?

DR. STORER: Correct.

DR. ANDOW: Then in terms of dispersal, from place to place, is that handled stochastic?

DR. STORER: That is also stochastic, yes.

DR. ANDOW: One last point, in terms of your dispersal -- in terms of your dispersal kernel, what is the shape of that kernel?

DR. STORER: That's a two dimensional normal distribution modified by tractiveness (ph) of the various different fields.

DR. ANDOW: Thank you. So the only point I would make is that insect populations, when you build stochasticity into the vital parameters, you get a certain amount of variation from year to year, but there is a component of environmental stochasticity that can be built into models as well.

As far as I can tell none of the models we are looking at here have environmental stochasticity built into them. One easy way to do that is push the population size randomly every year in one direction or another.

Because insect populations fluctuate, a lot of it is because the environment is changing, so one way to model is to say, this is a bad year and so the population is cut back and this is a

good year in the population. So that there is sort of demographic stochasticity and then there is environmental stochasticity.

So far, most of our models have not handled that part, and then the other part --

DR. GOULD: Could I interject? Indeed, Nick has one part that is environmental stochasticity in terms of field assignments, which is a major part of the environment is that field assignments are stochastic in terms if you are going to change a placement of the fields and how close they are, that's also very important environmental.

DR. ANDOW: So I would say that the patch models assume a random assignment to fields. So a particular form of particular realization of a stochastic process.

So that to some extent having explicit spatial model and randomly assigning fields is going to be very similar to what you get with the deterministic patch models.

But that's -- I guess I'll have to come

back to that.

So, to summarize so far, there is the issue of discreetness versus continuousness. I think models are appropriate there on stochasticity, there is still issues of stochasticity explore.

This is the other point, the population dynamics models on all of the models are relatively simple population dynamics models and the exploration of other aspects of population dynamics hat has not yet been done. Those are sort of general limitations of all of the models.

Now, in the case of the low dose events, there are certain elements of the population dynamics that could be important, whereas that very from the high dose events.

And for example, the actual population sizes coming out of the Bt field versus the non Bt field can have fairly substantial impacts. So it is probably worth exploring those things.

Then to get into the details and maybe to go through it, and maybe combine question C at

this point, and sort of go through the different parameters and the assumptions that they are making. Is that appropriate?

DR. PORTIER: Let me ask a couple questions, Dr. Andow and Dr. Caprio, and please Dr. Gould, feel free to jump in.

I want to try to understand these models, because I don't think we have yet answered the question that EPA has posed to us, which is what would you say is a good model versus a better model? Let's put it this way we won't call it a bad model.

I understand the discreet time event model, no problem as compared to continuous time event model, stochasticity in any model can be enter in any number of ways, so even discreet time models have rate constancy.

In this case, are the rate constants probabilities? That's what makes them stochastic?

Okay, so I understand that. In addition, you can put prior distributions on a variety of parameters that are part of the model

and when you were talking about field characteristics and the kernel for movement, that is, in fact, a prior distribution for parameter that goes in a model?

Am I correct in an assuming that? So then I'll ask you the question, in general, the more stochasticity that you put into a model, given equivalent models, one which is deterministic and one which is stochastic, with exactly the same basic format, would you agree that the stochastic model is the better choice?

DR. ANDOW: No, I would not. The stochasticity -- it is important that stochasticity is in the model where stochasticity is likely to have effects, not where it doesn't have effects.

And so for example, if you look at the populations size that we are tending to deal with corn rootworm, even under -- in the Bt corn we're still getting very large populations in the field with the 20 to 30 percent survival say in a one acre field you are still getting thousands of

beetles.

Now when you get thousands of beetles it means that, essentially, the population size is so large the demographic stochasticity is going to have very little influence on any of the results you can possibly imagine coming out of that model.

So it is really unnecessary to build in demographic stochasticity into many of these models. What we do know is that, or what we believe, is that the movement may be important. And some of those movement events may be rare events, in which case then we would be concerned about building stochasticity into the movement process if, in fact, the rare event and one can sort of look at these models and look at their intermediate output and find out how many individuals are actually moving to find out is this rare enough that it is going to be stochastically variable enough.

But anyway that would be the way to approach it. I think there are some parts of the model that it is unnecessary to have stochasticity

and, in fact, make it more confusing in terms of having to think about it as opposed to eliminating that from the model.

DR. PORTIER: Dr. Gould.

DR. GOULD: I agree with Dave completely that adding stochasticity where you have very large numbers and don't have anything is not a useful scientific enterprise.

But I think if you look at stochastic models that have been built especially for the movement parameters and field placement and things like that, you will see you get very different answers than you get with a general model that assumes two patches.

I think it is worth -- one of the reasons I was trying to get Nick's paper to be part of the record, if you look at his rootworm model, you see that especially with small refuges and other things, that the stochasticity enters in dramatically, so I would not dismiss that.

I would agree with Dave, when it is not necessary a stochastic model is not any better

than a deterministic model. But when it comes to situation where there are some rare events and possibilities, that's important.

We have to recognize that we're dealing with an insect that has strong population structure at least in some areas of the United States, it seems like, where it moves less -- you have to recognize that we have millions of acres of corn with thousands of subpopulations and that's kind of place where stochasticity could matter. I'm not saying it does, but we in the business here of risk assessment, not of coming up with heuristic models in some cases here. I want to move to --

DR. PORTIER: Let me give you my comment on this. I have some concern with your comments.

So most of what we have discussed is, then expected time to failure, if you really want to call it that. And yet we haven't discussed the probability of failure in an expected time, which is another characteristic that should be, I think, used in the risk assessment process. Without

competence to stochasticity in the models, it is impossible to calculate that probability all you can get is the expectation.

DR. ANDOW: I would differ a little bit on that point, because as you were pointing out you could use priors. I don't consider building in priors to be building in stochasticity the model.

So one can use prior distributions and the posterius result to get some idea of variation based on what we know as opposed to stochasticity which we might just build in a certain amount of noise that could generate additional.

In any event, I think when you have a -- if you have something such as population size which is so large, and you are looking at the stochastic nature of births and deaths when have you such a huge population, that population tracks the expected value very closely.

And the reason why it doesn't sort of track that is not because of the stochasticity of the demography, but it is because of other things

that aren't in that model. So I think will is still a good argument to eliminate certain amount of stochasticity.

But before, I just wanted to signal that other big issue we need to address here is the use of space versus non space. I think some of Fred's comments were sort of mixing the two together, stochasticity versus space.

And I think we'll get to that in a little bit after we finish this discussion.

DR. GOULD: I want to make this point. I do think it is an important aspect of a spatially explicit stochastic model, there are these two things.

I think Dave is correct. We could mix these a little bit too much, stochasticity in the space, stochasticity in demographic parameters. I guess what I wanted to get at in Nick's model in terms of small numbers, and what happens. All of our models are looking at single allele cases and typically going towards the end towards the high dose and this is history precedence.

I think if you ask the question, and you are asking how appropriate are the models, I think we're -- we're looking at this fine tuning. We can get into our academic discussions and loose track of the fact that all of these models are single locus models and there is a good reason for them being single locus. Because when you are dealing with a high dose, the only kind of an allele that can give you any survival, is an allele that confers more that 25 fold resistance to the heterozygotes.

That's very important to understand. When people have looked at how common those kind of alleles are, they are not very common.

So what I want to introduce is the fact that when you are dealing with a moderate dose, we're dealing potentially with having a lot more alleles, that if you have 60 percent survival, any allele that gives you 65 percent survival at that dose, is selected for.

So you can have potentially a polygenic kind of trait that you are dealing with, and it's

a very different kind of situation. I want to add to that we have one case of release of transgenic plants where we have a moderate dose for helicoverpa zea. Studies that have been done by J.R. Bradley, his students, I've collaborated with it. Published information shows that there is quantitative genetic variation for adaptation.

I think if we want to ask what is the appropriate model we at least need to consider the fact that we're over here on this one extreme looking at single allele models when we have to ask more about quantitative genetic variation, the populations and Bruce was getting at that.

DR. ANDOW: Before we switch from stochasticity argument, we'll come back to the discussion, yes, I would like to make sure that the panel finishes off the stochasticity discussion.

DR. PORTIER: Dr. Caprio.

DR. CAPRIO: I think we're also forgetting another form of stochasticity, or what I have termed uncertainty, which is really

related to our uncertainty in those input parameters and that's one of the things we have been trying to look at, is finding ways to systematically or to formalize that un certainty that we have on these parameters. It is sort of related to sensitivity analysis but it does as you mentioned come out with an answer of what is the probability of lasting for a certain time frame.

It is related to stochasticity in the model, but it is related to our uncertainty and how certain we are in these various parameters. If we are fairly certain in a parameter, we can make a relatively narrow distribution for variation in that input parameter.

If we're less certain about it, we increase the variance and then we -- the way we have been doing it with it the corn rootworm model I have been working on is just randomly -- each run of the model we randomly assign parameter models based on these distributions.

And then run thousands of simulations

and look at how many of those meet a time frame or the distribution of those results. And that adds stochasticity into it, but it is different than what we have been talking about right now.

DR. PORTIER: Dr. Andow.

DR. ANDOW: Just to clarify. I think what we were referring to there Mike, was this idea of using prior distributions and then looking at the subsequent posterior distributions of the output parameters.

So that would be a very important thing to do. The only models -- there are no models in this package that look at the problem that way. A previous model that you have worked with is one developed by Terry Hurley, and that was built up in that way.

I think sometimes he referred to that as stochastic, but it is really not stochastic, it is dealing with uncertainty.

DR. PORTIER: Can I ask a question on that? Then I want to get back to another issue. Do any of the modeling approaches use true basion

prior techniques?

A resampling technique with a rerun of the model is more of a marginal rather than a posterior distribution.

DR. ANDOW: I would say that Hurley model is set up to do that, but the iteration process has not been done yet.

DR. PORTIER: Dr. Caprio.

DR. CAPRIO: In the corn rootworm model that we're working on, and this is not for Bt, this is for methylparithion, we use that basion paradigm to look at the likelihood of initial gene frequencies, something that we can't go back and measure.

They are set up to be able to do that.

DR. PORTIER: So you are using something like a markup chain Monte Carlo to get the posterior from the resampling.

If this is technical, then I'm sorry.

DR. CAPRIO: No, we're not doing that.

DR. PORTIER: But I think that would be useful. It is true in my field as well. We do a

lot of modeling where we do resampling up front and just present the results of the resampling as the variation in the predicted term.

And that's not exactly the same as getting a posterior distribution which statistically is a stronger finding.

DR. CAPRIO: Right.

DR. PORTIER: Now getting back to the birth, death process and I'll pick on that one for a minute, because it seems to me, again, I have to go back to my experience which is in cancer modeling.

In cancer modeling the selection that goes on is for an extremely rare event. We're look at 1 in 10 to the 8th cells that has to be clonally expanded out to actually produce the tumor. That is what most of the model looks like.

Even with that many cells around, all of them are pretty much normal except this one rare event. And failure to consider that as a stochastic process actually does have implications

on the probability of failure or probability of getting cancer.

Is that not the case here for rare allelic resistance frequencies? Dr. Andow.

DR. ANDOW: It can be the case for the allele frequencies, but we tend to be handling those as frequencies rather than as numbers and we're dealing with the population size as a separate parameter.

And the population size numbers in the minimally thousands and upwards up into the hundreds of thousands. So, stochastic variation in birth death process would be like trying to model, of those eight million cells what is the likelihood, if you know that the growth rate of sells is X, how much variation are you going to see around that million rather than the rare events.

So the rare event is important to model stochastically, but the common events are less important that way.

DR. PORTIER: So if I understand it,

what are you doing is the stochastic nature of it is whether or not the rare allelic frequency mates.

But once have you done that pretty much the growth of the population becomes a deterministic process which we have also worked on.

Dr. Gould and then Dr. Caprio

DR. GOULD: We have had quite a bit of experience of high dose models using stochasticity.

My sense is it is not just whether that allele ever gets to mate the first time and if you run models with very high doses where you have very rare events, you often get extinction region wide of the resistance allele. Which is not something you get when you do frequencies.

I have done a lot of very deterministic models and you have a gene frequency hanging in there below one individual population for very long time.

I don't want -- this is all for very

high dose kinds of modeling when you have rare events. I want to emphasize you are all correct academically to have these concerns, but it changes a lot when you are dealing with 60 percent mortality instead of 99.9 percent mortality of susceptibles.

DR. PORTIER: Dr. Caprio.

DR. CAPRIO: I was going to comment or correct Dave, in that I think the store model, I certainly know the ones that Fred has worked with are essentially individual based models, in other words, there is either an allele out there or it is not out there.

As Fred mentioned extinction gets to be, when you deal with these high dose things, is a big problem.

So there are go very different ways. And that's one of the reasons why I got into the stochastic modeling is looking at gene frequencies 10 to the minus 14th and saying that resistance is going to evolve in that. It is incredibly rare that that gene or that allele would survive in

that case.

So there are two very different ways to handle it. One is frequency and population size. The other are people who are actually doing what are individual --essentially individual based models, and counts of individuals and genotypes of individuals.

I'm fairly sure from looking at Nick's paper that he has actual counts of individuals.

DR. PORTIER: Anyone else? Dr. Hubbard.

DR. HUBBARD: I have one comment that I planned to mention during the refuge section, but it has to do with modeling. I think it follows up on Dr. Gould's comments fairly well.

Organophosphate soil insecticides applied in seven inch bands or in furrow or in combination there have been used there for more than 30 years without a structured refuge and without the development of resistance.

The production of beetles from traditional insecticides ranges from 27 percent of the untreated checked to numbers greater than the

untreated checked with the high production of beetles one could conclude that tradition soil insecticides are low dose, and have a built in refuge which produces susceptible adults.

The question then is whether beetles produced from fields treated with soil insecticides experience a low dose of insecticide or no dose of insecticide.

Although the dogma of beetles being produced from insecticide treated fields coming from roots outside the treated band may be familiar to many of us, I'm not aware of literature documented yet.

Sutter, et al., 1991, the manuscript cited by Dr. Storer, in the document that was passed out yesterday did not include this conclusion in the abstract. I was not able to find the whole manuscript in the literature, but we do know that the normal behavior of older larvae is to migrate to new nodes of roots as they come out of the stock.

That would bring them into the

insecticide treated zone. Recent data my group has collected seems to imply that western corn rootworm larvae may require these younger roots to complete development to adult stage.

I believe that is likely that all beetles emerging from ground treated with soil insecticides have received a sublethal dose of insecticide. Translate that into our current dissections, a low dose.

In any event, I believe that this system is important to understand because resistance has been delayed for more than 30 years. If modeling efforts could focus on simulating why the soil insecticides system has worked so well, perhaps, a better understanding of the adaptation of transgenic events could be garnered.

As mentioned by Dr. Whalon yesterday, it is possible that selection place on larvae exposed to Cry 3Bb1 may be low. We do not know, but this scenario of delaying resistance to soil insecticides as a low dose may delay resistance to MON 863, also a low dose.

DR. PORTIER: Other comments? Dr. Andow.

DR. ANDOW: I just wanted to see if there were any other comments directly on the stochasticity problem because it's a new issue that is being brought up, and if not then we can go, sort of, to the next issues.

DR. PORTIER: If we could just summarize the stochasticity, I guess we would summarize it to say, that some is good, don't get carried away, and that given equivalent models one fully determine and one with well thought out stochastic variability included into it, that the stochastic would be preferable. Because it will give you a broader range of prediction with a probability included.

DR. ANDOW: Primarily because of the variance that you get out. So you would want to have the variances reported.

DR. PORTIER: Correct. Are we agreeing to that?

DR. GOULD: I would agree with that.

DR. PORTIER: So now let's go to the second half of this. Dr. Andow.

DR. ANDOW: There are a couple more issues even before we get to the pesticide one.

So Dr. Gould brought up the issue of single alleles as being the basic underlying assumption. He pointed out in some occasions it arises out of the high dose considerations, but also out of the consideration of taking a worst case scenario.

Because under the single allele cases will always result in faster evolution than the multiple allele cases or the quantitative cases.

DR. GOULD: I would like to take exception with that when I can.

DR. PORTIER: Dr. Gould.

DR. GOULD: That's true if the allele frequencies are the same, but the driving force and quantitative genetic variation and response is additive genetic variance.

When you have a high additive generic variance of multiple alleles response is much

quicker then when you have a very low gene frequency of a single allele. So I would say it all depends on whether you are talking about something that is initially starting with the same amount of additive genetic variance from a single allele versus a multiple alleles.

You might expect a more rapid adaptation with a single allele, because additive genetic variance increases very rapidly as frequency increases, and not with the additive case.

But that's not always true. I think there is plenty of evidence in Indler's book on natural selection in wild populations would show that.

DR. ANDOW: To respond, I think what I'm talking about is underlying the genetic lying architecture of the resistance trait.

I think what you pointed out is that under the quantitative case, the assumption is that the gene frequencies are quite high.

If you are to put the single allele case at the same gene frequencies to the same additive

genetic variance, you would find the single allele case would give faster evolution.

DR. PORTIER: Dr. Caprio. You wanted to jump into this.

DR. CAPRIO: I will point out quite a while ago, I was using a two gene model and was comparing the case of resistance with monogenic versus the two gene model. And in the absence of a refuge, you got exactly what you would expect, that resistancy evolved the same whether it was two genes or one. But in the presence of refuges the two gene model took much longer to evolve. Apparently that movement of susceptible broke up linkage among those genes. So there is in this question, I think, some impact of refuges that at least from my experience is more negative for polygenic resistance than it is for monogenic resistance.

DR. PORTIER: Dr. Gould.

DR. GOULD: We have worked a lot with two locust models and comparing them with single locust models, and I agree we have those same

results when what you wind up with is interactions between the alleles. When you assume an additive model of interactions of the multiple alleles in the two locust model you get the same result as you get with the one locust model. It's a whole issue, I think Dave brought up too, if you keep the additive genetic variance the same in the one locust model and the multiple locust model, they evolve at exactly the same rate.

The whole thing about the single locust is that because single allele is having such a major effect, you don't have a normal distribution of your variation you have bimodal, or whatever, distribution which gives you more additive genetic variance.

We have to be very careful when you make the comparisons of a polygenic model to additive model. I just want to finalize by saying we're dealing with a moderate or low dose effect where you're not expecting as much epistatic interactions among the genes. I can't

tell you what you are going to get. You have the possibility of more alleles. I think we have to be careful about that if we're doing risk assessment.

DR. PORTIER: Let me jump in a little bit. I don't think the issue we're discussing is, in fact, devoid of Dr. Hubbard's comment, in the sense that the data that he cited, the suggestion he has made concerning potential low dose effects from chemical insecticides could well inform the question we're asking on modeling.

So we haven't stepped totally away from what he was saying.

One thing that bothers me in the entire discussion we have had up to this point, we're focussing on polygenetic versus single allele effects, polygenic versus single allele effects, and yet we haven't talked about the mechanism of action of the agent that we're looking at.

What its targets are and some idea about looking at those targets and potentially deciding whether, in fact, we might have a polygenic form

for the target, if it is a cellular receptor of some sort or it is a specific cellular process that is governed by a half dozen proteins.

Snips in those proteins, potential other more complicated polymorphisms, in those proteins and the genes that make the proteins may well lead to the resistant allele you are looking for.

I would think that one could also target some mechanistic research in terms of the effects in the insects themselves to try to decide what potential mechanistic model might play a role in terms of the identification of the resistant gene type.

Dr. Hellmich.

DR. HELLMICH: Most of us in this room are used to the high dose model like Fred has commented on. The entomologist in the group are always trying to figure out, well, what are the parameters that are most important and what is the research that needs to be done that is driving that.

In the past it has just been gene

frequency, heterozygosity, movement have been important parameters. I'm getting the sense that some of these, such as movements we discussed yesterday, is not as important as it is with this low dose.

So my question is what are the important biological parameters getting at some of what you are talking about that we get into when we get into this polygenic, low dose situation.

Are there things that we should be exploring that we aren't?

And I, so far, I haven't found anything that is concrete that we need to do. We need to get more information on this, this and this.

I'm coming away from here saying or thinking that there is no research, biological research, that needs to be done relative to this product. I can't believe that's true.

DR. PORTIER: Dr. Andow.

DR. ANDOW: I think that we're supposed to be addressing that specifically in part C here, where we talk about specific things.

In terms of addressing the single allele case, I guess I would like to try a summary -- not a summary but point out that a lot of the work that has been done on the genetics of resistance would suggest that it's possible that there is -- that there would be a single allele in this case. It is also possible that there will be multiple alleles.

And in terms of which is more likely, I'm not sure I would be willing to put my money down, but I certainly wouldn't -- I certainly wouldn't be willing to bet against either of them.

DR. PORTIER: Is that a consensus, that at least addresses the likelihood question? Dr. Caprio.

DR. CAPRIO: I think that it's an old paper now, that Dave Heckle put out. He listed something like eleven different potential mechanisms he's kind of thinking about it. And a lot of those come into play when you have a low dose.

We are so used to thinking about these

receptors and so on with high dose products. This low dose opens up all sorts of possibilities that we would not normally consider.

We have some of these colonies that have 50 fold resistance and broad based cross resistance and so on, that we don't normally think about with high dose products.

I think we have to remember, like Fred has pointed out a number of times, when we are dealing with a low dose product, it's a different ball game. It is hard for us to really -- we don't have the experience to know what is most likely in this case.

So it makes your charge to think about possible mechanisms difficult because there are so many potential mechanisms and we don't have experience with these to know which are most likely.

DR. PORTIER: Any the other comments? Dr. Gould.

DR. GOULD: I want to give some credence in what Bruce was bringing up in a lot of detail.

I think that's a very good research idea. We are paying more attention to Bts and resistance management than we have to soil and insecticides.

Maybe people wanted to get rid of soil insecticides because they didn't like them, I don't know. The thing is to go back to that research question and ask, is there really a refuge or is that something we have dreamed up in that case.

The same kind of question can then be posed with these Bts again we haven't gotten the data. I think the discussion yesterday about knowing what the selective differential is, again, to get back to your question what is the research agenda we'll get to it later. I don't want to diverge too far. But just, at least, to respond to an important comment.

I would also go back to Nick Storer's model that is on the docket right now, what he did to validate his model is gone back to the cases of resistance developing to insecticides, looked at what the selective pressures are, look at what his

population structure is, and see if his model predicted what happened with the insecticide resistance and nicely, I guess I would say, it did so that's somewhat similar to what you are asking.

DR. HUBBARD: The case that he documented were with high dose products though.

DR. GOULD: I think you have to be very careful with what you call a high dose product.

Could you tell me what you meant by, those are high dose products?

DR. HUBBARD: I would consider crop rotation a high dose, because everything that is laid in soybean fields dies unless there is a weed or something there. Every beetle that tries to grow on soybean roots dies, so I would consider that a high dose.

DR. GOULD: Let me respond to that. I think what we know is that there has always been or data indicates there has always been like a low proportion of two year diapause before selection. Right?

DR. HUBBARD: For northern corn

rootworm.

DR. GOULD: That's fine.

But when you say it is a high dose, it's a high dose in terms of surviving on soybean roots. It is not a high dose for the northern corn rootworm in terms of being able to die pause for two years.

So the genetic mechanism around it, I think we always have to get away from thinking of direct adaption, there is indirect ways around things and that is one of them is to wait two years.

They didn't evolve to adapt to feed on soybean roots they adapted to have a higher proportion of the individuals diapausing for two years.

Now with the western corn rootworm, the issue is the way that they deal with this is they go into soybean fields and lay eggs. You consider that a high dose, because if you don't go into the soybean field, and then you have soybean roots to feed on, again it is a high dose.

But do we know that no individuals were going into soybeans and laying eggs before that it was indeed a high dose in that way? I'm not sure that the selection would indicate that.

But I think it is important to look at these things carefully.

DR. PORTIER: Dr. Hubbard.

DR. HUBBARD: Just a quick reply.

I think that Dr. Chang, when he looked at the amount of natural populations that contained extended the diapause, it was in the range of zero to two percent.

So that's in the range of a high dose perhaps. Maybe not quite not the 99.99 whatever. So there was some there.

You are right. We don't know the proportion of western corn rootworm adults that laid eggs in soybeans previously or outside of corn previously.

DR. GOULD: I'm bringing this up but not to completely criticize, I think there is a lot to be learned from looking at these comparisons.

We have an insect that seems to have adapted a lot to insecticide. We know it is capable of this because of its potentially, its population structure. Understanding that would help us. I agree with you on that part.

DR. PORTIER: I think you are in agreement. I think are you both saying that there are other avenues of data we could look at to help inform this modeling exercise.

DR. ANDOW: I guess I would like to move to the space issue. Is that okay?

And I'm going to connect it a little bit with the stochasticity issue because we have a spatial stochastic model versus nonspatial discreet models.

The first part about stochasticity in space is the grid size is really important. So Dr. Gould's comment and Dr. Caprio's comment, that in some of these stochastic models that allele goes extinct. In large part that's because the grid size is small.

Now, if you want to figure out how to

calculate how rare an event a spatial stochastic model can actually model, if you think about dispersal events, those are basically limited by the number of cells.

So if you have a rare event, and you have a 30 by 30 grid, then you are talking about 90 cells. So you are talking about on average things that are rare on the order of 10 to the minus 2. Things that are rare on the order of 10 to the minus 3, you would have to see lots and lots of runs of this to have the likelihood of picking it up. It will appear as an aberrant event.

So if you want to get rare and rarer events picked up, you are going to have to do more and more runs. But the problem with small grids is that there is a wrap around effect.

And that that can make it so that the rare events are less likely to appear than you would expect just by replication. So that's something that would need to be investigated if you are concerned about rarer events then 10 to

the minus 2 for a spacial grid associated with dispersal.

Now, if you are interested in the issue of population size, then you multiply those grids by the average population size and anything that is on the order of rarer than that, for example, if your average population size is one thousand, and have you 100 grid cells, then basically events that are occurring on the order of rarer than 10 to the minus 4 are not going appear in those models.

Again, you have to worry about wrap around effects in order to get rare events. If you are talking about things that are occurring 10 to the minus 5, 10 to the minus 14, you are going to have to be very concerned about the scale of the model itself. Because there are some event that just won't happen.

The mathematicians deal with this by treating the spacial grid as an infinite grid. Events as rare as you can possibly imagine can be appearing in the mathematical results.

DR. PORTIER: You lost me a little bit in there since I would assume that as you increase the grid size, you have to adjust the appropriate rates for dispersal to cover the fact that you are looking at smaller discreet units, and that as you go to an infinite grid size you are actually going to partial differential equations.

That's where your discreet event time model is going to take you. That would again take into account the issue, so I don't see why that becomes a problem.

DR. ANDOW: Actually they go to infinite lattices. They don't go to partial differential equations, because partials are actually approximations of infant lattices and they eliminate the effect of a lot of rare events. The thing is that the grid size does limit how rare an event you can expect to be thinking about in that particular stochastic model.

That's the fundamental point.

DR. PORTIER: Dr. Caprio.

DR. CAPRIO: I would like to clarify. I

think what Dave was assuming was by changing that grid size, you can either be simulating a finer and finer spatial network or you can be looking at a larger and larger area population.

Each patch remains the same size, but instead of looking at 100 you are looking at 1,000. That's where you get more individuals than 10 times the individuals. And you have more likelihood of picking up rare events.

And so there is a -- you can do it either way, make it more fine scaled or make it much larger scale.

DR. PORTIER: Dr. Gould.

DR. GOULD: I just want to agree with David. There really is a limitation in stochastic modeling at that level. Steve Peck's model, what Nick Storer's model is based on when dealing with very high doses can only start out at initial gene frequency of 10 to the .03 or .01, or else you always get extinction. This was in a lattice of 1200 or more fields.

So yes, when you are dealing with

regions of a million and asking what is going to happen, it is important to look at that. However, the stochasticity does, you need to take a look at that, because when you are dealing with those low probability events and you are making them deterministic you lose a lot as well in terms of that assessment.

Because what was shown in those models is that the patchiness over multiple regions and the stochasticity in terms of spatially, where those fields are don't call it stochastic, call it random or whatever placement really has a big impact.

We're in that same boat where you guys were asking us about what is a high dose. Here with are talking about deterministic stochastic models that would be a great discussion for a panel to dealing with something that was coming in for a high dose.

I'm not sure it is as relevant in this discussion, because of what we're talking about.

So I think there is a whole academic

area that you could take a course in, in terms of the argument between modelers who are doing these empirical more stochastic and deterministic models.

I don't know how far we want to go with it. I think maybe this is enough.

Although, I think that the key point I was trying to make is even in these models, if you build in stochasticity, and you are trying to make conclusions associated with that stochasticity. You have to be concerned about how rare an event you can actually be thinking about.

You can't be thinking, again, with a small grid, you can't be thinking the about a very rare event.

So I think that's just the main point.

DR. PORTIER: Any other points on this question?

DR. ANDOW: Then the more general question about space versus nonspace, I think the issue has to do with to what extent do we need spatial models and what do they get.

I think there are several things that if you take average gene frequencies in a spatial model, that they will tend to give similar results as the nonspatial model.

But what space allows to you do is it allows you to investigate very specifically how the location of fields may be effected. So questions like, does the refuge stay in the same place is a question you can answer with a spatial model that you couldn't answer with a nonspatial model.

A question like how big of a column of Bt fields becomes a focus for the essentially, the evolution of resistance is a question you can ask with a spatial model that you couldn't ask with a nonspatial model.

It is important to understand what are the new questions you can ask and to make sure that those are the question that you get information on. Not just sort of redoing the same old questions over and over again.

DR. PORTIER: Dr. Gould.

DR. GOULD: I want to reiterate, I agree with Dave that some things, the spatial model is not useful for, but for questions about farmer compliance, for questions about where those -- whether some farmers are adopting and others are not, the spatial model gives you different results than the deterministic model.

So in some cases you get resistance developing in the spacial model and you don't get resistance developing in a deterministic model or advice versa. So those are pretty important differences between the two.

DR. ANDOW: On the compliance issue, we see that there are issues of compliance. One is are they actually planting the percentage that is asking for? The second are they planting it in the right place?

You simply can't answer the question about what is the effect of planting it in the wrong place with a nonspatial model.

That's where you get the differences between the two models is primarily on that side

of the question.

DR. PORTIER: Any additional comments on part B?

I'm not going to summarize the stochastic nature discussion again.

But I will cover the last few. I think we noted that there is data out there that could be potentially useful in looking at these low dose effect types of events in trying to create better models.

We talked about the use of potential mechanisms as a guiding tool actually biological mechanisms that drive the toxicity in the species. And then as a general rule, in terms of deciding what level of complexity you want in a model, define your questions and that helps to define which model will actually proof to be better, the spatial issue we were just discussion is one that is clearly part of that entire paradigm of modeling.

Shall we move onto part C?

Let's go ahead and do question C. Do we

want to go down this list of parameters? We have to have the question.

MS. ROSE: Please comment on the appropriateness of the following input parameters of these simulation models for corn rootworm protected field corn, resistant allele frequency, dominance of the heterozygote, movement of the males and females mating and ovipositional behavior and other genetic and behavioral parameters.

DR. PORTIER: I will note that many of these issues we have discussed in great detail in parts of the other questions that could be pulled into this question.

We don't necessarily have to get into that same discussion all over again just because it is at this question. It is just informative to the panel. Ms. Rose.

MS. ROSE: As a point of clarification, specifically on the models we have currently, because that's all we do have to work with and a little bit more of the appropriateness of what is

currently available for decision making.

DR. PORTIER: With regard to these parameters.

MS. ROSE: With regard to these parameters and what appropriateness of the outputs of these and the agency's review of them, based on -- there are some big differences in some of the input parameters, as far as resistant allele frequency, dispersal, and because of some of these differences of what we have to work with now because it will take time to refine the models, what is the appropriateness -- what came -- the outputs of these based on the inputs, if that coming out correctly.

DR. PORTIER: Dr. Caprio.

DR. CAPRIO: My impression is as I have stated before, I think the models despite all these differences and dispersal parameters, wide variety of parameters that are employed, give the same sort of general frame work in terms of resistance. I think there is surprising agreement among the models.

DR. PORTIER: Dr. Andow.

DR. ANDOW: Mike, did you do some work and inbreeding and those models were also similarly robust with respect to these parameters we're talking about, with these results, these outputs?

DR. CAPRIO: Some place they were going to make a copy. I did an inbreeding coefficient of zero and an inbreeding coefficient of .1 and approximately has it on to resistance. I don't think we know what sort of inbreeding there is in this particular insect.

DR. ANDOW: The reason I bring that up is because one of the issues that is not extremely well addressed in any of the models is this idea of the 10 day delay in emergence. And that would an appear, I think, the easiest way to model that is within inbreeding coefficients.

That's why I thought Mike's point was -- Mike's results would be particularly relevant.

Everybody was given a copy of the table that Fred passed out to try to compare the

different models. I guess, if we are to look at sort of the starting resistance frequency, we have already gone over that as could be quite important if, in fact, resistance is quite common now and that would sort of change the whole discussion and texture of the discussion.

DR. PORTIER: To ask a pointed question. So let's stick to that parameter for a minute to ask appointed question, the two different values used were one in 1,000 versus 1 in 10,000.

DR. ANDOW: They are all rare.

DR. PORTIER: Do we have any information that would advise the agency as to which one of these is more likely to be correct or we just don't know. Dr. Andow.

DR. ANDOW: I would say at this point it could be even more common. And I wouldn't know for sure, but if some of the work that has been talked about earlier, specifically Lance Meinke's work, may shed a lot of light on that as to whether or not we're even in the right ball park here.

DR. PORTIER: So would be fair then for us to advise the agency that for this parameter a sensitivity analysis would be very informative on both models, and that sensitivity analysis might be weighted towards greater resistance allele frequencies than one in 1,000?

Is that a general consensus, I see some nods. Dr. Gould.

DR. GOULD: I think the 10 to the minus 3 or 10 to the minus 4 is based on some data for lepidopteras pests where the assessments have been made, in terms of what allele frequencies are.

But, I guess again, the issue of low dose and the ability -- there might be lots of different alleles at single low size, many low size is very important to consider in reevaluating it.

If we look at a lepidopteras pest, the diamondback moth, which has a different biology, there seems to be more of this polymorphism you were mentioning in India where there is a study published in the Journal of Economic Entomology.

Before any selection pressure with Bt, there were certain isolated populations that were over 100 fold resistant. So it was just a fluctuation in a polymorphism in that case.

But I think having a little bit of data, it wouldn't take too much of a study to show that the initial gene frequency was at least less than 10 to the minus two, it wouldn't take very much work to do that and that would be very helpful.

DR. PORTIER: As a flip side to just doing -- I'm trying to address the issue. I don't know if that was what you were looking for Ms. Rose, in terms of some guidance for this parameter.

MS. ROSE: Being that we don't know the initial resistance allele frequency, I appreciate the recommendation that the research be conducted to identify that, but in the mean time is the 10 to the minus 3 or 10 to the minus 4 a conservative enough, appropriate enough parameter to be working with until we get that information.

DR. GOULD: For risk assessment?

MS. ROSE: For looking at the models used thus far.

DR. PORTIER: As it pertains to IRM.

DR. GOULD: For risk assessment, I would say I like Mike Caprio's approach of asking what our knowledge base is for assuming that. And then using a model that uses that as your distribution for asking where the risk is.

That can be done, so you develop a model that looks at what the potential is for it being higher, using that as your mean and then having a variance around that, you could do something likes that but not to just assume that's it.

DR. PORTIER: If I could, Dr. Gould try to get you to answer the question in the condition that they will use one of these two models.

DR. GOULD: In the condition that you will use one of the --

DR. PORTIER: What are the three models you are considering?

MS. ROSE: Andow and Onstad, the ones that I summarized yesterday. They are in the

Monsanto submission, the modified Caprio model, the Andow and Onstad model, and then Onstad's model are the ones thus far that have been developed for the corn rootworm.

Pretty much they are using .0001. From what you're saying is that none of them are appropriate if we need to go above and beyond that. So, should we not be considering any of these models at this time?

DR. GOULD: That doesn't mean that you shouldn't be considering the model. I think Nick made a strong point of the idea of looking at relative effect as opposed to years to resistance.

I think if you look at relative effect of these techniques, especially with again the moderate dose, you are going to see that by lowering the gene frequency all the models are going to tell you it takes a little bit longer to get resistance, but they are not going to differ that much.

If you try these models at different gene frequencies you would get a difference in how

many years it takes for resistance to development, not that relative amount.

But if what you are concerned with is how many years, yes, then it certainly is important to consider others. But in terms of throwing out the models is different than throwing out the actual runs that have been done, and ask those people who have the models to do more runs for you with a different frequency.

That's not the same as throwing out the models. It is just throwing out that parameter. And I just hope that you will consider the Storer model since it is another contribution here. I hate to harp on this it is just that it is more detailed and as much as we have heard that sometimes stochasticity and spatial parameters aren't important, sometimes they are. In this pest it might be.

I would like to make a comment about this table. The reason I put some effort into starting this, at least, is so that we can make some head on head comparisons between the models

and that has been avoided for quite a while.

This is not a complete chart. It is based on what I could do. What I would appreciate is input from the panel on where I'm wrong. I also did not have access to the Monsanto parameters, unfortunately, before I came here, so those could be added here, and just take a look and see what parameters you actually have in those models.

Also, I didn't put in what all the results were and compare the results, but I think at least having this in the report will give people a sense we have done our task on that.

DR. PORTIER: Dr. Andow.

DR. ANDOW: The question on resistance allele frequency is it is probably useful for the risk assessment process to look at higher initial gene frequencies. In terms of dominance of the heterozygote, I think that the range that has been looked at is either quite recessive to sort of intermediate or additive in the Onstad model.

In the model that I worked on with Don

Onstad, the values tend to be on the order of not that recessive .05 to close to additive, but doesn't get up to additive. So they are the on the recessive side.

On the modified, the Monsanto modification of Caprio's model it looks like it goes all the way to dominance. I'm not sure how low they went on that case. So now what is the appropriate thing to do? Well I guess everybody knows that if the resistance is more dominant, it will evolve faster.

So if you are interested in worst case scenarios, then the more dominant cases would be worst case scenarios in terms of what is likely, that is another question that I'm not sure where to come out on this point, except that the literature seems to indicate that when it -- resistance requires less of a resistance ratio, then there is a greater range of dominance values that you see.

So as you get higher and higher levels of resistance, you tend to see lower, more and

more recessivity.

So that it is appropriate then to explore a wider range of dominance values for this particular case.

DR. PORTIER: Is this a case where Dr. Caprio's point about the 11 mechanisms may play a role in helping to guide you as to what might be an appropriate dominance?

DR. CAPRIO: I would have said the empirical evidence that Dave mentioned, in terms of what we have seen in selected colonies and so on that as the overall resistance ratio decreases, at least the genetic dominance is much more variable.

So we can expect if we were going to set probability ranges around this dominance value, I would make it much broader for this low dose event.

DR. PORTIER: I'm thinking about for this particular low dose event. What type of data could guide us into choosing a better dominance value? Dr. Hubbard, you had some comments on

this yesterday. No?

DR. HUBBARD: I --

DR. PORTIER: I wasn't going to let you get away, right away, because I know you had some data yesterday in terms of selection pressures. I'm wondering if any of that would be useful in helping decide, potentially, for what degree of dominance there might be.

DR. HUBBARD: I'm not a geneticist, and I can't comment on that.

DR. PORTIER: Dr. Caprio.

DR. CAPRIO: I guess the point we're trying to make is that because of the dose, there is a much -- this is an unknowable parameter until resistance evolves.

Asking what value should we plug in here is the wrong question. I think we should talk about the variance, or the expected variance, or the uncertainty of that parameter.

I think that's what we're trying to say is the uncertainty is much greater because it's a low dose event that the question you are asking,

what value should we put in, I think is one we're trying to avoid because inherently we're more uncertain about this.

DR. PORTIER: So, I guess the recommendation to the agency on this particular parameter is that it could range from completely recessive to completely dominant, and we just don't know.

Again, conditional on this model. Because if it is polygenic we are maybe not even talking about the right thing. Is that what we're saying? Dr. Andow.

DR. ANDOW: I would say there is a bit of a central tendency so it's not like we are looking at a uniform distribution. If that's what you're getting at.

DR. PORTIER: Your prior would be to put some additional weight towards the .5?

DR. ANDOW: Yes.

DR. PORTIER: Okay.

DR. HUBBARD: My only additional comment is that there may be -- it may be more likely that

there is multiple genes for -- in host plant with corn rootworms and European corn bores quantitative traits with multiple genes are often see in host plant resistance and those are low dose events generally and may be similar to what we're seeing here.

DR. PORTIER: Is this being helpful? Do we want to continue moving through the individual parameters here, movement of males and females?

Anyone on the panel want to take on that parameter? Dr. Gould.

DR. GOULD: I was looking at that when I was going through the models for these questions.

I guess the differences -- the important differences, if you were dealing with a high dose, would be the movement of males before females are mated with those.

And the models range from having almost no movement of those males to having random movement from what I gather from the Monsanto model.

Again, I have not seen that so I didn't put those parameters down. With a high dose model, that can make a major difference. I think it can even make somewhat of a difference at a moderate dose, but not as much.

And then if you look at the Storer and the Onstad model, I guess, I may have put something in here for the premating dispersal that is incorrect. This is just a preliminary, but in the post mating dispersal, they are not too different in terms of what their assumptions are.

They base those assumptions on data from some empirical studies. But I don't know what part of the country those studies were done. Looking at the Spencer paper last night, that looks like it is a completely different kind of thing.

So I would say these models have data based on very few studies, if only maybe one. I'm not sure. So you might want more information on that.

DR. ANDOW: In terms -- to add to that

list, the model, the Andow/Onstad model is essentially assuming that there is no premating dispersal of the females and there is random postmating dispersal of the females. And the males sort of disperse as they will without distinguishing between the first versus the second mating.

I would also like to add that preliminary work that I have done on varying this does bear out some of the comments that Fred and Mike were talking about yesterday, in terms of how sensitive is the model to this.

It's a little bit, but you don't get huge differences really varying this too much. Part of the reason that you get it is that basically, if you were to look at the population sizes in the two patches that -- because there is high survival in the Bt patch, there is an a lot of beetles already there.

Generally, the gene frequencies are a little bit higher there, because the selection intensity is not a lot higher, so you don't get

huge differences in gene frequencies. The effect of dispersal really is to carry some of the genes from one place to the other.

But because you already have a lot of individuals in both fields, and the gene frequency differences aren't hugely different, the effect of that movement is less, because it's essentially -- you know you have to see movement of genes so that after the movement you get different gene frequencies for the movement to have a big effect on the evolutionary process.

When you have lots of individuals in both fields and you don't have huge differences of gene frequencies in those two fields it is not going to be -- the movement parameters have got to change a lot in order to get really different gene frequencies after movement. That's just a general property of these types of models.

DR. PORTIER: Any other comments on this?

DR. HUBBARD: Just to follow up on Dr. Gould's comment, just that it may be appropriate

to have different input values for the eastern corn belt than the western corn belt.

DR. PORTIER: I was going to point out that we covered much of that earlier in our previous discussion, that the lack of knowledge of what is going on in some of the other corn rootworms is something that plays a role here.

Mating and Ovipositional behavior. Any panel members want to comment on these? Dr. Caprio.

DR. CAPRIO: I'll just mention again from our empirical work with heliothines that ovipositional behavior can impact the source sync dynamics and in doing so impact population dynamics and can under some circumstances, particularly if you start talking about infield refuges, be important to know something about ovipositional behavior.

How far these females are moving and where they are putting their reproductive output, whether it is transgenic versus nontransgenic fields.

DR. PORTIER: But in terms of these specific models is there anything we can say about the parameters that have been used and the way in which they have been used, that can guide the agency as to what might be the most appropriate for these -- conditional on these three models.

DR. ANDOW: My understanding, again, not knowing exactly what is in the Monsanto modification model, but an assuming it is very similar to what Mike had before, is that the models are assuming local random mating.

As I was pointing out before, this issue of local inbreeding may be fairly important as Mike just pointed out with an inbreeding coefficient of .1 you get 50 percent change in the rates. So that could be considered substantial. So yes, I think that that would be an issue that would be wise to look into.

DR. PORTIER: Do all the models allow you to do that?

DR. ANDOW: Not by simple parameter changes, but they can be done. I don't see

anything that says that it wouldn't be simple for -- maybe not simple, but there wouldn't be a relatively straight forward way of doing it in any of these models.

DR. PORTIER: But that would require a change in the model?

DR. ANDOW: Yes.

DR. PORTIER: Again, I'm trying to stay to conditional one, assuming you are giving this model to your sister who might not be a computer expert and mathematician and say -- and they want to run it.

Again, what would you tell them about the parameters on these issues? I'm trying to make it -- trying to really focus you narrowly into this question for these models.

DR. ANDOW: On these models I would say you couldn't run it.

DR. PORTIER: Dr. Gould.

DR. GOULD: Again, in the Storer model, what you have is that delay in emergence. And as an interesting finding there that indicates,

probably, a lack of inbreeding because of that delay.

The insects are protanderous, so the males come out early. So the males are coming out in the refuges earlier than the males are coming out in the Bt plots. And those males at least in this model therefore have movement and are moving into those plots and they are not relatives.

So, it goes in two directions in terms of this inbreeding when you have delayed development in a protanderous (ph) insect.

I would say that actually the Storer model addresses this. It does allow for random movement within a field. I think there is a movement within the field, but since the males are coming in from outside the field, I'm not sure when there is that developmental delay if there is a problem with inbreeding.

DR. PORTIER: Dr. Caprio.

DR. CAPRIO: I'll just point out that there is two different levels of inbreeding that we might be talking about, which is within the

individual, which is sort of what we're talking about with specific developmental delays.

But there is also a broader issue of inbreeding and what might be viewed as genetic variation between populations. That somehow we look at an overall gene frequency. In fact, one would expect in these populations that are not highly mobile that there would be considerable variation and by chance some of those populations will have much higher frequencies.

DR. GOULD: I would say the Storer model does address that by having this unit. I agree with Dave, if you extended that to have a million fields instead of 2000 fields you would have more variation.

The Peck model addresses that too. Actually it was surprising, the Peck model even with holding back movement that by allowing the initial gene frequency to vary before you put out the resistant plants.

It didn't vary that much. It wasn't dramatic. I was somewhat surprised if we knew

more about this beetles' movement in the western states maybe we would expect more.

I would agree with you it needs to be done. But we do have the models to start doing that. It is not as if the current models can't do that.

DR. PORTIER: Any other comments on this parameter?

Ms. Rose, do you have other genetic and behavioral parameters? Are there any specific you want to get into? Have we addressed these important issues for you?

I guess I would characterize our discussion up to this point with regard to these parameters to say that each of the models have different aspects that are good and bad to them.

The only way you are going to get a really good feel of what this might mean in terms of insect resistant management, conditional on using these models is to try some of the variations we have talked about where you can in each of the models, and use some judgment from

what comes out of the models; would the panel disagree with that conditional on using these models? Any disagreement with that sort of broad, very broad summarization? Dr. Gould.

DR. GOULD: I would just add to that. Going back to the fact once you're dealing with moderate dose these models do not, even with all these little things, the models don't differ that much because they are not sensitive to much in terms of a moderate dose.

We can work all we want on all this fine tuning, but if you don't have a high dose event, I don't know why we're wasting our time on that somehow.

Maybe I'm wrong, I don't want to exaggerate it. You could have density dependent stuff going on we don't know enough about density dependent mortality in these models, for the larvae and all that.

Somehow, I think we're playing a game, like we're dealing with a high dose thing and worrying about these things.

MS. ROSE: I do have a couple points of clarification, but just on your last comment, Fred, are you saying you don't think the models have much utility at all for a moderate dose? Am I hearing that?

DR. GOULD: I guess what I'm saying is, I could build you a model on the back of a napkin that would give you pretty much the same results a lot of these models would in terms of a moderate dose.

That the answer is pretty straightforward typically. So, I know -- I think they do have relevance. I think they are they are basically telling you that because of our uncertainty and the lack of data to go into them, we have a lot of uncertainty risk assessment.

It is not saying anything about the models being bad. We're talking about trying to worry about parameters in terms of varying them, where maybe it is not as important at these moderate doses.

I think I could show you this by showing

one of Nick's overheads from yesterday.

DR. ANDOW: I would prefer not frankly, because it is on a log scale it doesn't reveal that fine scale.

DR. GOULD: I think I could deal with that Dave, because if you wouldn't mind.

DR. ANDOW: Go ahead.

DR. GOULD: I don't think it will disturb us too much. I think it will show you the answer to what you are talking about a little bit.

DR. PORTIER: You had some other questions?

MS. ROSE: I'm not sure if the other points of clarification are as relevant after Fred's last comment. But there are some other aspects. First of all if the panel recognizes any worthy of discussion. But also parameters such as refuge being fixed, or random placement of refuge, and also the -- I don't know that only one of if three models considered in infield refuge, the necessity of looking at infield versus external and some of those

parameters if the panel could discuss some of those as additional.

DR. ANDOW: Aren't those in the next question?

MS. ROSE: The next one is just insecticide.

DR. ANDOW: The next part of the question is on insecticide, but the fourth question is about refuge and refuge placement.

MS. ROSE: If you feel it would be more appropriate we can discuss some of those things. But we were thinking in terms of the input into the models themselves and the importance of the consideration of these parameters for one thing in these models.

DR. PORTIER: Dr. Andow.

DR. ANDOW: In terms of how the models deal with fixed versus random or placement of refuge, any of the patch models treat refuge placement as random.

You can only go to the fixed models if you have some sort of spacial structure in the

model. The same with the placement of the refuge, you need spatial structure in the model to get there.

So, if you have any questions associated with those, only models that deal with spatial structure explicitly can handle those questions.

DR. PORTIER: Ms. Rose, let me get back to the original point. I think Dr. Gould's response is not going differ from much of the rest of the panel on this regard, in the sense that -- I get the feeling you are trying to seek from us some feeling about in what situation what is the best model to use.

I think what you are getting back from the panel is the concept that we are not going to support any of these models per se, because they all have flaws from the basic point of this is a low dose event versus a high dose event and they are developed for high dose events.

I don't think we're saying they are not useful. I think we're saying there is a lot of aspects to all the models that you can't just

choose one and say this is clearly the best. And I think that's the problem. So our answer to the question about random field placement is going to be that there is only one model that allows you to do random field placement and you are going to have to rely upon the predictions of that model.

Because the others can't help you with that prediction. And we don't know how important it's in this case because we're not confident with any of the models with regard to this particular issue. Is that sort of the general concept?

DR. GOULD: We have to say we're confident about the models. What we're not confident about is the parameters which you are putting into the models.

If you knew what the parameters you could put them into these models and they would be very good. But we keep saying we don't know what the parameters are to put int.

DR. PORTIER: That's a slightly different point than I was making. On the

previous discussion when we talked about the actual functional forms of the models, you had considerable concern about some of the aspects, the basic assumptions, that go into these models.

And you are presuming that a new model which uses assumptions that might be more appropriate to this case is not going to be fundamentally different.

I don't know that we can presume that.

DR. GOULD: That's what I'm saying, before you know the parameters, I wouldn't say that the models are -- I agree with you on that in that way it depends on how you phrase it.

All I'm saying we know so little about the parameters that are important here, you can't expect the model to give you a good answer if you don't put in good data. I wouldn't be as critical. I think the models for what they are made out to be we would rely on them. It's a different perspective. I'm stuck.

DR. PORTIER: Dr. Andow.

DR. ANDOW: I guess I would say the

general point is that there are a lot of structural differences in the models in terms of what they include, what they don't include.

We think that changing that will have some effect on the output. But how big of an effect it would be is -- you would have to see some very big changes in some of these models in terms of their parameter values to get those big changes.

And that in general, some critical issues they are all communicating about the same thing, that if you are talking about resistance occurring starting from initial frequencies.

That's probably the key one. If you are starting from the low initial frequencies you are talking about on the order of 15, 25 years for a lot of parameter values.

That's sort of a key point. So if it is more common, then of course it is going to be lower, if resistance is more common, the time to resistance will be faster.

DR. PORTIER: Dr. Hellmich.

I'm trying to get somebody else into this discussion.

DR. HELLMICH: I understand that these one locust, two allele models are like that because computationally if you get into multiple alleles or the low side it is very difficult. It seems like we need some polygenic models here.

I know animal breeders have been using quantitative genetic models for years. Are there other models that we could fall back on that would be more appropriate for these -- for this event?

DR. GOULD: I would imagine that quantitative genetic models would be fine for this kind of thing. We're not talking about something sophisticated here, when you ask what are the research questions, they are not that sophisticated.

We just need to get the data on what the additive genetic variances in the populations and then plug them into a quantitative genetic model -- it is not even a computer simulation model. Just to get a feeling what response to selection

might look like. It is not the biggest deal.

DR. WHALON: Can I introduce at this point another point that is germane, I think.

DR. PORTIER: Dr. Whalon.

DR. WHALON: Just a caveat, I would reference the discussion we had yesterday on mortality events and the behavior along the root grazing et cetera. Some input that we had from some of the documents that were provided regarding root exudates and hypothesized high dose in some areas, et cetera.

As we talk about these potential multigene quantitative genetic effects we're really talking about trying to understand what the multiple mechanisms for mortality are among first instar larvae affected by these plants.

I see that as an area that could be fruitful in terms of additional research and just wanted to insert that in this discussion as something that could be done.

DR. PORTIER: Dr. Andersen. You have been trying to get into this.

DR. ANDERSEN: It's all right. I think that what the panel has come to has given us some pretty good guidance about what we can do with these models and some of the limitations of them, in the sense that these are models at high dose and we're probably looking for what we need to have a model that more realistically mimics this situation where we have a low dose, or a moderate dose, at least not a high dose.

And that has been useful to really clarify for us. It also -- I'm summarizing for you, but I do think you have given us some advice how we can use the models we do have.

Either now or in the future I think we're going to be looking at an appropriate model for this situation.

DR. PORTIER: Good. I'm trying to move us forward because we're going to be bogged down on this question for another hour if we don't. It sounds to me like we have given you the general advice you are looking for.

Any final comments for the panel on this

question? Dr. Gould.

DR. GOULD: I want to make something clear. If you are thinking these are not relevant, please don't take as a take home message.

The thing is some of the extreme parameters in all this debate, that's why I was worried about getting into this debate, it is academic.

All of those models are pretty relevant in the range of .6 mortality and all give you the same answers that's not to say that the initial frequencies are wrong, but most models are pretty relevant in that regard.

You don't need a whole bunch of different stuff. We're talking about it is easier now for any model to give you an answer at those frequencies, at those mortality frequencies. These models, don't throw them out they will give you quite the answer you want. You could make them simpler and they would give you the answers.

DR. ANDERSEN: I think you have given us

good advice, and we wouldn't throw them out. I think what we're try to go get to is that we may be somewhat beating a dead horse to actually try to make these particular models a whole lot better.

We may really need to look at substantially different mechanisms, something like the quantitative genetic models that you are talking about.

DR. GOULD: They won't give you that much of a different answer. Where you need the information is on the parameters, all those models are going to give you pretty similar answers even the quantitative genetic models at those levels. Maybe people want to disagree with us, but I don't think so.

What you need are the parameter estimates. You put those parameter estimates in those models and then you have a -- don't put all your work into coming up with any new models, that will take us two weeks and we'll have it for you.

What you need are parameter estimates

which will take you years to get.

DR. PORTIER: Any other comments from the panel? Dr. Andow, any last comment before we move on?

DR. ANDOW: I was going to point out that the key parameters involved in a lot of these models including the high dose models, is essentially, one could characterize it as the fitness differential and we were talking about this last time.

And the difference with high dose models is that there are parameters that modify that fitness differential that are involved in the details of the ecology. And as you get to the lower and lower dose models, what happens is that the prominence of those modifications of selective differential decline in importance, and the prominence of the selective differential rises in importance.

Which is why all these other parameters have less influence. That's why all the different models are giving essentially similar results

despite the variation is because the key thing is to look at the relative fitness between the RR's and the SS's with a little bit of modification for the RS's.

DR. PORTIER: I'm going press on and we're going to finish this question before we take a break. That will hopefully make you be very articulate.

If we could go to question, part D on question three, please.

MS. ROSE: How does insecticide use in the refuge and or Bt fields affect the predictions of time to resistance.

DR. PORTIER: Dr. Caprio.

DR. CAPRIO: Paul, did that table ever get copied?

DR. LEWIS: Yes, it was distributed this morning. I think everybody should have a table with a title page from Dr. Caprio.

DR. CAPRIO: I'm not sure where it ended up. But in any case, basically --

DR. PORTIER: Do you want to just go

ahead?

DR. CAPRIO: I'll just explain what it said. I looked at different refuge sizes and various amounts of insecticidal use in those refuges, and the default assumption has always been you know, if you take away 50 percent of a 20 percent refuge, it is going to act essentially like a 10 percent refuge there is a little bit difference because there is a little more Bt product out there. I would just say in that table if you looked at a 20 percent refuge with 50 percent mortality due to a spray, you have essentially the same number as if you had a 10 percent refuge if you had a 50 percent refuge and got 20 percent survivorship after the insecticide.

You came reasonably close for a 10 percent, the same values you got for a 10 percent. This is more impact because there is more Bt crop.

It seems -- if you pull out those individuals out of that refuge, you are decreasing the relative size of that refuge compared to your

transgenic crop. And it is going to have an impact, it will hasten the evolution of resistance.

DR. PORTIER: Dr. Andow.

DR. ANDOW: I will not disagree with that assessment for these low dose event.

DR. PORTIER: Dr. Whalon.

DR. WHALON: I have a question relevant to that assessment. Do we need a larger refuge given the principal of conservation?

DR. CAPRIO: I think that will come up in another question when we discuss refuge, but I think it is relevant given this -- I think we need to remember this discussion when we get there.

DR. PORTIER: So what stands if you are going to spray the refuge, you are going to decrease the time to resistance.

DR. CAPRIO: Correct.

DR. PORTIER: Dr. Gould.

DR. GOULD: I just think we need to address the other part of the question of or Bt fields if you are spraying in the Bt fields, what

is the effect of that?

Is that addressed already?

DR. WHALON: Could I introduce a thought that is relative to that?

It strikes me that you have two different situations here. One situation is a recommendation or at least in the materials that we have got from the understanding of EPA to Monsanto's proposal for an IRM, that they would allow seed treatment in the refugesea.

And that other insecticide treatments based on economic injury level and IPM monitoring, et cetera, would be applied uniformly to both the MON 863 and the refugesea.

And at least that's my understanding in this context. Is that what you are addressing?

DR. GOULD: I guess there is a lot of biology here that is important.

You have to ask what the interaction is between the Bt and that insecticide use.

If we're talking about the refuge having very high population densities and having density

dependent mortality, adding a density independent factor if that is how the insecticide works might not lower the population that much. I'm not sure what it would do.

But in the case where Bt is acting first or after the insecticide you would have a very different interaction effect. If you are starting with a low population that already does not have density dependent acting, then you might have a different effect.

Again, I would say we don't have an estimate of those parameters and that would be useful research to do.

I think we could more easily answer the question what would be the effect of just spraying the refuge or just treating the refuge answering the question of treating both and then a question of just treating the Bt ones and not the refuge.

I think that we need more research on that.

DR. PORTIER: If I could ask a simple question. Aren't most of your concerns that you

have just discussed dealing with the magnitude of the effect, but wouldn't 1 argue that in most cases, in most scenarios you could think of, if you treat the Bt fields you are likely to increase the time to resistance, you are not likely to decrease it?

DR. GOULD: I think in a risk assessment perspective, I think I would say that the likelihood is on that side, I agree.

We might be surprised by the biological data and therefore it is not so hard to collect that data. We ought to know that, but agree with you, yes.

DR. PORTIER: Dr. Caprio.

DR. CAPRIO: The real relevant question though was pointed out is that they are talking about you have to treat both refuges and Bt fields. And if that -- the default assumption in doing that is that that insecticide has the same impact in both those patch types.

If the impact of the insecticide is dependent, is very different in the Bt field than

the refuge, then that can be an extremely relevant question and it may not go the way you would think it would.

DR. PORTIER: Under what condition would it not go. So that if someone were looking to design an experiment to address that question, what condition can you think of where it would, in fact, not go in that direction?

DR. CAPRIO: When you get into these questions of density dependence and you are seeing either more mortality in the refuges. I think the case from cotton is that, in fact, you are seeing more mortality in the Bt fields because they are more stressed.

I think it is just something that we need to do research on and find out some of these potential interactions.

DR. WHALON: There is another scenario may be that we haven't -- not to muddy the waters still further, but what we have essentially in this MON 863 event is a differential success generating mechanism among species of corn

rootworm as well.

So where you have overlapping species, you may favor one species over another. Hence, actually exacerbate a change in management strategy in the time frame we're talking about.

DR. ANDOW: I would like to address the question of how insecticides might get different results depending on -- I have been thinking about this in the context of the corn bore issue. But I think it translates into the corn rootworm issue.

If we think specifically about adulticide applications of corn rootworms and -- or if we think about insecticide applications while the adults are out there and those insecticides may have adulticide effects even though they weren't aimed at the adults.

So you might spray something that -- against the corn bores, for example, that also has adulticidal activity to the rootworms or you might spray something against spider mites that also has adulticidal activities.

And if you spray say something that has

-- adulticidal activities that is sprayed early in the emergence period of the rootworms, it is going to be selective on the rootworms. So the later emerging rootworms are the ones that are more likely to be resistant at this point in time.

If you kill the early emerging ones, then you are essentially giving the resistant types an advantage. If you spray something late in the emergence period, you may be differentially killing the resistant types in which case you may be delaying resistance further.

I think that the timing issue could interact with the genotypes, resistant and susceptible genotypes, in such a way as to either accelerate or delay resistance.

DR. PORTIER: Any other comments from the panel on this question? Is that clear?

DR. ANDERSEN: Yes, thank you.

DR. PORTIER: Okay. Let's go ahead and take a 15 minute break and come back and start where we were supposed to start this morning with question four.

(Thereupon, a brief recess was taken.)

DR. PORTIER: Welcome back to the SAP meeting. If we could have the first of our remaining polyploried (ph) questions read to us, starting with four A.

MS. ROSE: There are actually six subsections to the refuge questions. EPA has concluded that a 20 percent refuge is adequate to delay resistance during a three year period. Part A, please comment on whether this refuge strategy is adequate to delay resistance.

DR. PORTIER: Dr. Hubbard.

DR. HUBBARD: I'm going to repeat a little bit, and still try to be brief. MON 863 produces a number of survivors.

The root tissues express the endotoxin at levels below the LC 50 for newly hatched nondiapausing corn rootworm larvae, and a little above the LC 50 of an average of 10 field collected populations.

Changes in larval feeding behavior on MON 863, ie the grazing on the exterior of the

roots versus tunneling inside may enhance survivorship on MON 863. The exterior of the roots may contain lower dose of Cry 3Bb endotoxin, but this has not been documented. As evidenced by the large number of adults produced, the low level of endotoxins in the roots relative to the LC 50 and perhaps facilitated by an altered feeding behavior, susceptible survivors are likely produced from MON 863.

Corn rootworm management tools which may be classified high dose such as, crop rotation, broadcast use of cyclodiene insecticides sprayed for adult control, all have resulted in the development of resistance after ten, 15, 20 years. But none of these were tactics that were employed with an internal or an external refuge.

Organophosphate soil insecticides have been used for corn rootworm for more than 30 years without an outside structured refuge aimed without the development of resistance.

With the high production of beetles one could conclude that tradition soil insecticides

are low dose and have a built-in refuge which produce susceptible adults. The scenario delaying resistance to soil insecticides as a low dose may delay resistance to MON 863, which is also a low dose.

Additional factors favoring the likelihood of delayed resistance include the delayed emergence of beetles from MON 863, increasing the likelihood that susceptible males immigrate and will compete favorably with resistant males for resistant females.

Problems exist with the plant. It may be tempting for growers to plant a refuge on fields previously planted to soybeans because of reduced corn rootworm control costs.

A mechanism should be in place to document prior crop history so that the refuge indeed produces adult beetles. The management plan put forth by Monsanto states that the refuge should have the same management options or practices and cropping history but did not put forward a mechanism to document this.

In summary I an agree with the conclusion of the rest of the NCR 46 committee, that the probability of rootworms developing resistance to Cry 3Bb1 during the interim registration period appears to be low.

DR. PORTIER: Dr. Whalon.

DR. WHALON: I don't know how this is a question of procedure -- how best to include a lot of the discussions that have gone on before. And maybe I just ought to preface some of the things that have been said in the other areas by saying ibis, then I am in a sense, covered and introduce a couple other points. Is that, okay.

DR. PORTIER: Yes.

DR. WHALON: I think that the goal of the refuge is pretty obvious it is to ensure adequate production of susceptible beetles and encourage their moving into the transgenic corn produced beetles such that there is intermating.

I think that the panel has low to moderate assurance that the 20 percent refuge will accomplish this given all the parameters

associated with it. I, some what tongue and cheek, it's not a high confidence, in the sense of a high dose confidence.

Generally from my perspective, the suggestion that one can see resistance early enough, given the kind of scouting tools that are out there right now, I think is not an appropriate conclusion.

And in fact you need better tools or maybe alternate ways of thinking about it. And I think some of our discussions yesterday are relevant to that arena, especially sentinel crops.

I think that the agency's documents appropriately have identified other tactics, and these have been mentioned by Bruce and also in previous discussions. They include crop rotation and other strategies for insecticide management, and those are key components of this strategy.

A second key issue in any IRM strategy is the effective estimation of the selection intensity in that, and that discussion was held already and should be abridged in here where

appropriate.

I do think that there are some critical research needs and those also have been mentioned variously, but especially in the area of monitoring and detection and development of putative resistant strains and I will come back with further comments under the other sections. Thanks.

DR. PORTIER: Dr. Hellmich.

DR. HELLMICH: I don't have a lot I want to add to that, but given that the presentation that Nick gave yesterday showing that there is a pretty low response curve with refuge, that you don't really get that much of a gain going from 20 to 30, 40 percent.

I think that the in this case, the refuge, 20 percent refuge recommendation we have with corn bore is compatible with this. And if we're looking for simplicity and the potential of stacks in the future, I think that it is good to get a refuge out there that won't be changing.

In the past, when the problems we had

with the European corn bore refuge, is that there were mixed messages of how much corn growers should plant. I think that establishing a 20 percent now is good, because we're looking to the future. Especially given that changing it from to 50 percent, like I said before, wouldn't really give you that much of an advantage because of the low dose.

I guess there could be some question in the future maybe whether or not even a refuge is required in this case.

But we may not want to discuss that right now.

DR. PORTIER: Dr. Caprio.

DR. CAPRIO: I guess the simple answer is to take the question at face value and say will it delay resistance. I think a 20 percent refuge will.

I think you know as I look at the handout that I gave you, if you compare the difference between 10 and 20 percent versus 20 and 50 percent, there is much more to be gained going

from 20 to 50 percent.

Certainly if you look at the right hand column where you have zero percent survivorship in refuges there is clearly those numbers should be all identical for the different refuge sizes,because there is no survivorship in the refuges.

There are an example of what Rick mentioned with no refuges, and it clear that refuges do have a large impact.

So again, the question comes down to will it delay resistance enough. Will it delay resistance for 3 years? Yes. Will it delay resistance for 15 or 20 years? That's more questionable.

I'm not sure that it is an overly conservative plan in that vein.

DR. PORTIER: Any other comments on this question? Dr. Neal.

DR. NEAL: I guess I would like to point out that this is not a high dose strategy, so that the numbers of beetles being produced in

transgenic fields are going to be relatively high.

So in a high dose strategy, we're comfortable with 20 percent refuge because the numbers of beetles being produced, compared to those being produced in the transgenic field, are very high. So that the likelihood of intermating between resistant beetles is very low.

In this particular case, you have got a situation where there is not a lot of selection pressure coming out of the low dose treatment. So that you are going to -- if you did have an event take place where you had beetles that were highly resistant, they would also have a chance of intermating with nonresistant beetles coming from that same field.

But you also have a situation where in these transgenic fields you are going to be selecting for low levels of resistance. So 3 to 10 fold resistance most likely over time.

So in order -- if you are interested in preventing that low level resistance, then you are

going to need more immigration which would suggest larger refuge just from the fact that you have only got about -- you have got such a high survival in those fields.

So you have a lot more beetles. So you just need more beetles to compete with them.

DR. PORTIER: Dr. Andow.

DR. ANDOW: I would like to make a couple of points and the first point is that I agree with some of the previous comments, that this is not a conservative plan, scientifically speaking.

If I look at the 11 points that Monsanto made as to why it is conservative in their interim proposed plan I can identify the placement position that it should be placed next to the Bt fields, as a conservative piece to that plan.

Because of uncertainty we don't really know how far it should be, and that's a conservative decision, but of the other 11, I can't identify them as being conservative.

So for example, adoption while it is probably

true that adoption country wide will be relatively slow in the first year, the second year, at least based on the experience with the other Bt corn, it jumped up very quickly over a very short period of time.

Especially when you look at localized areas and similarly it could happen here. So that wasn't a conservative argument they were making. In terms of grower adoption, what we heard yesterday is that all of the growers would individually choose to plant only a small portion, maybe one of their fields to the Bt corn during the first year, and depending on what they found, they might increase it a little bit each year.

So that in terms of adoption, the long term piece seems to be that they want it consistent with the corn bore refuge -- but the short term piece seems to be that they are only going to be take it on individually a little bit at a time.

So that that piece really isn't a conservative piece either, and then the

insecticide piece I think has created -- Bruce's analysis of the insecticide piece suggests that it is uncertain to what extent the insecticides act as good models for either the fast or the slow evolution of resistance and it will take more research on the insecticide side to be able to demonstrate that.

So that using that using an uncertain argument to argue conservatively is -- it just doesn't hold.

So then the second point has to do with the interim nature of the plan and whether or not we're really dealing with an interim plan, I think is something that we should consider. Yes we are, in fact, thinking about it as a three year plan. But we also know from our previous experiences on these plans is that it is very difficult to change them once they get started.

So that it might be useful for the panel to be thinking about in not just for the three year period, but sort of if it were to stay this way for the whole time, is this a good way to take

the first step.

Now if it was going to change, we know that it would be very difficult to make it in any way more difficult for growers. So we couldn't go from like a 20 percent refuge to a 50 percent refuge very easily. It may be easier to change from a 50 or a higher percent refuge the a lower percent refuge. And, in fact, growers may applaud that as being quite -- a positive move by the government.

But in any event, we should note that change is not uniformly easy in both directions.

So if we're thinking about this in terms of its interim nature and what kind of changes are possible, we should be thinking about that and then the final piece on this interim nature in terms of my questions yesterday, to Dr. Vaughn, it was pretty clear that the approach is in the current proposed plan is to not stress through communication to growers that this is subject to change in three years.

I guess I'm a little worried about

putting all the chips on a particular plan that is not conservative at this time. And just simply -- but that's not to say that there aren't other approaches that could allow a temporary registration to go forward.

DR. PORTIER: Any the other comments from the panel? Dr. Gould.

DR. GOULD: I'm almost afraid to introduce this, but I'm having a pretty hard time with this whole business. I guess it comes to this point of is this adequate. That's what you said, adequate.

I feel we're being forced into making policy without the science, and I don't like this. I think the whole idea was that this was supposed to be science based policy.

What we have been discussing in the last day and a half is the fact that we don't have the science. We're lacking the parameter estimates, everything is based on some kind of an idea of what do we have out there.

When you asked is it adequate to delay

resistance, it is pretty vague question. Certainly most of the models will tell you any amount of refuge will make it delay it, but you don't need a refuge to not have onset of resistance in that three year period.

I think what Dave is saying is very important. You are setting a president. Unfortunately, I have been through this twice already with the bowl worm situation where somewhere we're forced in to come out without the science, come up with some estimate somebody has thrown out, and decide that that's okay.

Then when we try to move from a 4 percent refuge to 5 percent refuge in cotton, because as the data is coming up, we can't do it, because it won't happen. I think this president with the farmers is very important. For us to start without science and come up with some number like 20 percent seems to me if you want a policy, that's fine. But if you want a science based policy, we can't give you that.

I guess my feeling is we're not ready

yet. I say that it's not adequate. I think we should go back and get the science first, if you want a science based policy. If this is a question of just you want to decrease the use of organophosphate pesticides and therefore you want it out that's fine to make that decision. But if you want a resistance management plan, we don't have one.

All the data given here is sort of taking a high dose strategy and trying to throw some numbers in there and assume that you have it when you don't.

I don't think the emperor has any clothes here. I'm not willing to go on with this thing. So, that's the comment.

DR. PORTIER: Agreements or disagreements? Dr. Andow.

DR. ANDOW: I'm sorry. Why don't you get agreements and disagreements--

DR. PORTIER: Do you have a different issue?

DR. ANDOW: A slightly different issue.

DR. PORTIER: I think Dr. Whalon said to some degree the same thing you said, in terms of level of comfort with this issue being low to moderate at this point because of lack of science.

DR. WHALON: Well, first off, anecdotally, if that is a shy comment that Fred just made, I would hate to see a forceful one.

As I have come into this and listened to the process I'm inclined to agree in this context, that I think that we have to err on the side of conservation and the principal of conservation should rule here in this situation.

If the agency were to move ahead it is their decision whether to move ahead or not. As a science advisor in the process, I would say there are a lot of parameters that we don't have, a lot of uncertainty.

There are other areas that the agency makes decisions in that are not unlike this, so what I would say is if you look at the benefit side of this risk decision, there are significant benefits associated with this technology and

moving this technology out. There are also significance science advantages in moving it out in the sense that you can actually do monitoring and do things in the field, and I say that all with the caveat that if anything, we ought to err on the side of conservation if this moves forward.

DR. PORTIER: Dr. Hubbard.

DR. HUBBARD: The last point, especially, I very much agree with. Some of the science that is necessary to do depends upon large scale field studies being -- large scale field plots being available, and they are not necessarily going to be there unless the registration moves forward.

You need to have the quantities of seed available to do some of the studies that should be done.

DR. PORTIER: I just want to reiterate the point that we're not making a registration decision here.

DR. HUBBARD: I apologize.

DR. PORTIER: And that this is -- the question before the panel should not hinge upon the need for a commercially viable product in order for us to do large scale field studies. I think that's not that's not an issue for this panel to consider.

What we're here to consider is the scientific issue. And I think Dr. Gould has thrown a gauntlet in front of this panel saying there is not sufficient science to support the adequacy of this decision.

I think it is up to this panel to either counter Dr. Gould's points or agree with him and give EPA some sound scientific advice on this issue. Dr. Caprio.

DR. CAPRIO: I would like to echo Fred's comments, in that, I think given the adoption rates we're talking about, we have to remember that if we accept this interim plan, we are in essence, Dave's point is absolutely correct, we are in essence accepting that the maximum amount of refuge we can ever have for corn rootworm is 20

percent.

I think it is far too early in the process to make that decision. Given the low rates of adoption that one would expect, I don't think it is a decision that needs to be made right at this point.

I think we're much better off accepting a more conservative approach, and letting this ultimate decision take place after we have gotten more of the information that we need. I don't think it is a decision that we ought to be making right at this time.

DR. PORTIER: So I'm going to flip this over again and point out that Dr. Gould's comments about difficulties in changing the sizes of these plots again should not be something that enters into our debate on the scientific integrity of a management tool.

I think we need to consider to some degree the practical aspects, but again, I want to try to keep us on the scientific issues.

If we were forced today to look at this

question of refuge strategy, would you say that, no, the science is really not here and you should not make a decision?

Or would you say that there is sufficient science here to make a rough interim decision and here is what would be our best bet?

Or do we just say this decision is adequate? I'm trying to keep it into a simpler range here. Dr. Hellmich.

DR. HELLMICH: I think everybody agreed that more science in this case would be good. But in the discussions that we have had here, it is not clear to me what field studies we need to do, what exactly we need to identify.

In some cases, you can study this for 100 years and still not have enough science, and we have to be practical and say well is it good enough as a preliminary.

It is frustrating, because I just haven't had the experiments that we need to do in order to get this product out. It is not clear to me what they should be.

Granted, we need to find out what the gene frequencies are, whether or not there is any kind of heterozygosity. Those are still the questions we have with the cotton products. They are still the questions we have with the corn bore products.

I think that if we wait until all the science is necessary to make these decisions, we'll be here -- we won't be here. It will be our grandchildren that will be here, and there has to be some sort of balance.

I don't know how we get that.

DR. PORTIER: Dr. Hubbard, then Dr. Andow.

DR. HUBBARD: I agree with that. I wish to remind the panel that the western corn rootworm can arguably be considered the most economic pests in all the United States. There is more acres treated with insecticides for root worms than for anything else in the U.S..

If there is not an economic incentive to gather basic biological data on this insect, I

don't know that we're ever going to get this data because it is very difficult to do.

There has been a great deal of work that has been done on this insect. It is just -- Dr. Gould, is right in that there is much data that is missing, is because it is very difficult to collect.

Mandating that impossible data be collected; I don't think is something that should be done by this panel.

DR. PORTIER: Dr. Andow.

DR. ANDOW: You sort of gave three options: go with what is there, stop, or something else.

I would like to propose something else. This comes out of -- when for another crop in another country, when faced with very similar issues of a lot of uncertainty in the scientific information, grower acceptance being that they would start slow and build up depending on what they found, sort of a lot of grower input, and an expression system that wasn't high dose.

They decided and this is Bt cotton in Australia, they decided that we would limit in the first year plantings to 15 percent done each farm, and increase that to 5 percent every year, and then evaluate what to do.

For them, they stopped at 30 percent because the farmers felt that that was all that was reasonably supportable. But if you think about 15 percent of a farm when you are talking 2,000 acres, that's still a lot of land.

So there is a lot of -- and what they wanted to do then is to do the experiments and make the observations in that interim period in which they could then establish where they should end up.

I'm just going to low that one out use a different alternative to what we have been looking at.

DR. PORTIER: Dr. Gould.

DR. GOULD: Just want to address Bruce's issue, I guess about these experiments that are impossible to do.

I don't think they are.

To get to Rick's thing, I think two major ones are: what is the initial gene frequency, is there a polymorphism, what is the selection intensity. You brought all of those up, those haven't been done -- movement -- those can be done. They actually can be done without massive releases.

Those aren't the kind of questions the kind of questions where you need massive releases are the one that address the high dose question. To need 80 percent Bt corn to answer that those questions, I don't think is necessary.

What I want to remind you when there is pressure to do those experiments they can be done. There was a beautiful case with the Monarch situation. Everybody waived their hands around for a long time and then all of a sudden it was something needed to be done.

Within two years, there was good, solid, scientific data that nobody ever expected to see, and the results were surprising in many cases. So

I think that if somebody said we have for do this work before we release it, or they say if you don't get the data on Monarch butterflies, you can't plant that corn, then it will get done.

If we start saying, oh well, we don't have the data but we'll let this one slide, we have done that before, and whenever that is done we don't get the scientific information. I think it is time to say we need the science based risk assessment and we don't have it yet.

Let's get the science scientific risk assessment first then do the release.

DR. PORTIER: I think we're not going to reach consensus on this issue. I think it is quite clear you have a range of scientific opinion from -- this is as adequate as it is going to get because of the difficulties involved in studying science and getting the information you need to know you really have to get this.

It is time to draw a line, we really need to get this information before you make a decision.

Does that pretty much cover the range from the panel?

DR. HELLMICH: I want to make one point. I think that the opinion of the NCR 46 Committee, which was the rootworm experts, should weigh heavily here.

They are familiar with the issues. They know what the science that needs to be done and they have outlined what that science is.

I think that they are aware of, in most cases, the limitations of what the information is. They, as a committee, I think John said there was 14 members and several associate members, they think for an interim plan 20 percent is sufficient. Bruce, you are on that committee maybe you could comment a little bit more.

DR. PORTIER: Dr. Hubbard.

DR. HUBBARD: In the May 30th, 2001, letter to Dr. Matten, the NCR 46 did outline a series of bullet points of research that should be conducted. I think -- I'm not aware that -- I think the majority of these bullet points -- the

research is currently being conducted.

And I think probably that maybe there is -- we didn't have Dr. Gould sit in on that discussion, and maybe there is a few more bullet point that should be added. But I think that most of the really important data that we have identified we're going after.

DR. PORTIER: I'll speak for Dr. Gould. I think his point is that that's great.

Now, wait for that data before making your decision. Dr. Gould, would that be?

DR. GOULD: That would be pretty much what I would say, but also to get to Rick's point that we should rely on the people at that meeting. If we have a letter from them that says 20 percent seems adequate to us, if we had documentation about why, then we could judge whether they were the experts or not, or knew -- what was that based on.

It just seems like it's in the consensus that was made. I don't know how that judgment was made. Why should I rely on that? I'm not sure.

DR. HELLMICH: If we had members here we could ask them.

DR. GOULD: That would be fine. I agree with that.

DR. PORTIER: Dr. Andow.

DR. ANDOW: I would like to make sure that we know that Jon Tollefson, when he came to speak, said he was not going to presume to speak on behalf of all of NCR 46 and yet here we are trying to say this is what NCR 46 is saying and the reason he said that is because they agreed not try to speak on behalf of them all, because they all had different opinions.

So let's not try to force something on their joint opinion here and let Bruce sort of speak as much as about as he feels is appropriate.

DR. PORTIER: We can debate the issue, but again, I will point out to the panel that we don't seek consensus in this debate here.

Each of you are speaking for yourself and the opinion you put fourth is your opinion if there is consensus, I'm going to note it for the

EPA. Clearly here, we're not reaching consensus.

I think they are getting a very good feel for the fact that this is still controversial and that the decisions, the management decisions are not going to be easy ones because the science is not so clear to all the scientists involved, that the decision is an easy one. Dr. Caprio.

DR. CAPRIO: I'll reiterate that given the adoption rates that are projected by Monsanto, I don't think anyone is saying that we have to shut the whole process down. I don't think there is any reason that we need to make this drastic decision of 20 percent refuge at this time. I think there is plenty of room to do something like Dave says and do a graduated introduction of the product, get a look at it, see how it is doing on these farms and essentially put that final decision off until we have some more knowledge.

I just can't help but say that there is not enough knowledge now, so let's defer.

DR. PORTIER: I don't want to reiterate

arguments. Unless we're going to introduce a new argument here, a new point, I think it is quite clear that there is no agreement on the panel. Our write up will clearly indicate all the different opinions and different points that have been expressed.

So if there is a new point to be expressed, then let's go at it. Dr. Hellmich.

DR. HELLMICH: I just want to say in the past, when the academics couldn't agree on a refuge amount it seems like the default was no refuge.

And if we set that as a president, I think that would be dangerous because it could be interpreted like that.

I think 20 percent, because it is compatible with the corn bore refuge amount is a practical amount to have as a refuge.

DR. PORTIER: Dr. Andow.

DR. ANDOW: I was going to ask if any of the people that haven't expressed an opinion on this could, for the record, express an opinion if

they are prepared to.

DR. PORTIER: I'm sure none of them are shy that they wouldn't express their opinion. Everyone has been quite vocal.

Dr. Hellmich raised a point I want to follow up on.

It was something several of you said earlier about clearly zero is not a good idea for a refuge.

Does the panel agree with that concept at this time given the science that is out there?

DR. PORTIER: I'm seeing a lot of nods. I see one no, Dr. Gould.

DR. PORTIER: Zero percent no refuge. If they made a decision today and put no refuge out there, would you agree that scientifically -- that's a bad decision because of all the modeling exercises, because of what we have learned in other situations even though they are high risk?

Is the panel saying that zero would be a bad idea?

DR. PORTIER: I see a lot of the panel

members saying, yes. Dr. Gould.

DR. GOULD: I guess the reason why I say no, is Bruce just brought up the point that there may be no selection. Right? If there is no selection, you don't need a refuge. We don't know that so I don't know that it's a bad idea.

What I'm say is we don't have the science to -- if you want us to just come up with opinions, that's one thing. If you want us to come up with a scientific opinion, I don't think we have a basis to say that zero is a bad idea.

DR. PORTIER: Dr. Hubbard.

DR. HUBBARD: To quickly just agree with Dr. Whalon in that it is not a conservative approach to say that if they went forward at this time. But it is not a science so --

DR. GOULD: I would I agree it is not a conservative approach.

DR. HUBBARD: One other quick point to address. If you wish to assess the reasons for NCR 46 statements, it is part of the public record for this meeting.

DR. PORTIER: Dr. Neal.

DR. NEAL: I was just going to reiterate the point that Bruce made about the conservative decision here. The larger the refuge the more conservative.

DR. PORTIER: And the panel does agree with that to some degree. I think 100 percent refuge would be extremely conservative. Dr. Caprio.

DR. CAPRIO: If I could just bring up one point that Rick made. It is also in the NCR 46 is compatibility issue with the other Bt products. Again, the stark product isn't out there.

I don't think it is consideration we should be making at this point. It is very prominent in the NCR 46. We don't even have the stark product yet. That shouldn't be a consideration at this point, that can be when you make a final decision down the road, but it is not a decision that needs to be made now.

DR. PORTIER: Dr. Andersen, I hope we

have given you some guidance here. I think the strongest statement we have made is that zero percent refuge is not conservative. Scientifically, that would be supported whether we should choose zero is a different issue.

Then you have a broad range of opinions on everything else.

DR. ANDERSEN: Yes, I think that summarizes what you have provided us. Yes.

DR. PORTIER: Shall we move on to part B of this question?

MS. ROSE: Part B of the refuge question states: because the current plan being evaluated is based on limited data and is an interim plan, limitations to the total number of acres MON 863 might be considered.

If so, should the limitations be on acres planted per state, or per county, or on another basis during the time an interim IRM plan is in place.

DR. PORTIER: Dr. Whalon, I'll let you have a first stab on this one.

DR. WHALON: I would reiterate that the goal of the refuge area, even in the discussion that we have had today is the same, it doesn't change. That is to ensure adequate production of susceptible beetles in case resistance develops, encourage their movement into transgenic corn, swamp out any heterozygotes and hopefully homozygotes resistance that may develop.

So the key to the IRM is preventing excessive repetitive use of the MON 863 technology on a local scale and if the IRM is going to be successful, I think that's the focus.

One could presume two general conditions. One, the -- notwithstanding the discussion we just had, that an interim plan would be adjustable. Hence, I would argue that a conservative to a more specified approach would be the way to go as more information is available. If it were to be registered, or conditionally registered.

I also think that the issue of local scale, the issue of scale is one that we haven't

addressed and would be worth further discussion, perhaps at the end of this refugesea discussion.

And I have a couple other comments but I want to reserve those for a moment.

DR. PORTIER: Dr. Hellmich.

DR. HELLMICH: Putting caps on states, or counties, or whatever, that suggests there is going to be pretty heavy regulation in there. A lot of times in the NC 205 committee meetings and we talk about trying to get more -- or a handle on what is going on -- I appreciate Dave's comment that what the Australians are doing in cotton. But in that case, you have a few hundred growers, where it is not that difficult to keep tabs on what is going on.

But in the case of corn growers, we're talking about at least 10,000 growers that could potentially be involved with this.

I think that trying to keep track of something like that would be very, very difficult. Plus, who is going to be out there policing it? That's the other question.

I would like to think that we have had the growers here and invite them as partners and at least for an interim trust them. That they aren't going to be planting more than 80 percent of this product, because we're recommending 20 percent refuge.

I think that if you get too heavy handed at the very beginning, you lose the trust of the growers. If you don't have the growers on board, you might as well -- you have lost the whole gain of this -- you've lost the war.

And I think that bringing them on board as partners, as stewards of this product and educating them would be a better approach than trying to get heavy handed and say that -- put seed caps on this.

I think that that invites them to go across the county and buy seed some place else, go across state borders, you know there are ways of getting around this. I don't think we want to get into that.

So I would suggest at least on an

interim basis that we follow the stewardship and trust and see how far that gets us and then we can see. We're going to be keeping our eyes on you, a let's get this right.

Rather than trying to follow the Australian model, which I don't think would be practical in this case.

DR. PORTIER: In terms of this question, which is conditional on being limited, you are saying limit it to national scale with a particular percentage not cropped by this crop. That's effectively what you have said.

Dr. Hubbard.

DR. HUBBARD: This question may come from the portion of NCR 46 most recent letter that states "resistance evolves at the local level so the key to IRM during an interim registration period is to prevent excessive repetitive use of the technology at the individual farm level."

Monsanto's response to this question was that limitations are not justified given that a 20 percent refuge will be placed on every farm.

Because of NCR 46 comments and the comments of Dr. Whalon, et cetera, I would state that if additional restrictions were placed, it would be at the farm level and not at the county level.

It is that local farm -- and so it would just -- it wouldn't be a county thing, it wouldn't be a state thing, it wouldn't be a region thing. It would be how much can that individual farmer plant on his own farm.

My own personal opinion on this is not really science based. I think it is more agreeing with Rick, on more a practical base in that, I think in that beyond the 20 percent is not justified at this time given the science that is available. But that's not really science based.

DR. PORTIER: Dr. Caprio.

DR. CAPRIO: I agree that given John Tollefson's comments yesterday about dispersal and local use patterns that per farm basis is the most appropriate way to go.

DR. PORTER: Dr. Andow.

I'm going let you jump in this since actually brought it up in the last question, and see if you have a different opinion.

DR. ANDOW: Thank you, I guess from the science perspective, there is a lot of stuff we don't know. However we do know where the insecticide resistances evolved along the Platte River, in these localized areas along the Platte River, and that to a large extent that diffused out from there.

I had the opportunity to fly over the Platte recently, just seeing the landscape was just eye opening. And that basically, you have a strip along the Platte a few miles wide and it sort of budges in and out depending on where the irrigation zones are.

There are these little patches of crops. It is in these little patches where these resistance -- is where the resistance is evolving. If we're going to think about local levels, we could kind of specify at that kind of a level that it is more likely at that scale than any other

scale because that's where it happened in the past.

From a science perspective, that would be where I would -- that would be the leading hypothesis in my mind. Now on the implementation side, I guess I would favor -- I know that it's possible to monitor county level use because that's what EPA does for the other crops.

And it would also be possible to implement things at the farmer level. It would be harder to implement things at smaller than county level but larger than farmer level, so there are some constraints to how we think about that.

It would seem that the leading hypothesis would be a several mile by several mile area would be, if we're defining local that, would seem to be what we have in the rootworm case.

DR. PORTIER: Any other opinions on this particular issue? Dr. Gould.

DR. GOULD: Since we're not really talking about science but rather how we are dealing with growers and interactions I think the

Australian example is a very useful one.
I think this idea we have to allow 80 percent, to give the growers the idea that we are with them, may be a little misguided.
I think it was nice to have growers come in here and give us their opinions, but again, we're assuming this is economics by having the growers come in. You talk to the growers about what's going on, they can't individually once a product like that is out, not use it if the other farmers are.

But I think you have to look to economics to find out what benefit they are really getting from those products and if you are really with them.

Are you really with them by having them use 80 percent? Maybe you are, maybe it is going to decrease pesticide use and increase their health. I would like to know more about what is going on to make that kind of comment that the Australian example won't work.

Maybe you are more with the farmers by

saying, look we have something, we want it to last a long time. Work with us. We'll start out with a low amount. We will really test it well so you will have something sustainable that will be affordable over a long period of time -- because of the cost of pesticide things and new products goes down over time if they don't have to be reinvented.

Maybe that's when you are with the farmer.

DR. PORTIER: Any other comments on this issue?

You have got, sort of, two basic points of view. I must admit I'm more in agreement with Dr. Gould, and to some degree Dr. Andow's point of view, that potentially a phase in period would not be a bad idea, given the uncertainty in the science we're talking about here.

And while I'm not sure about the level issue, clearly that's a difficult thing for me to think about, but the phase in if I had to look at it -- certainly some of our previous comments

about geographical locations and potential differences in geographical locations in terms of the types of pest that are there, et cetera, should be taken into account in deciding where you place your scale experiments, your scale up of planting.

DR. PORTIER: Any other comment? I think --

DR. WHALON: I have a comment. I'm not sure that I heard the response in the way that you have summarized it.

DR. PORTIER: I'm say there is two basic responses here.

DR. WHALON: I would say that there is at least three. The first being no refugee because you don't implement the technology until you have the science.

The second being that you go with a 20 percent.

And the third being that you use some sort of graded conservative mode of implementation greater than 20 percent less than 100.

DR. PORTIER: You are correct. I'm reading the question literally in the sense that the question is conditional on us doing this.

But that is correct. The previous comments from the previous question about not moving forward until you get better science still obviously holds.

Any other comments?

Dr.Weiss.

DR. WEISS: Well, assuming that a refuge does go forward, if I look at this question, I think the question is how many acres should we limit that to. If we assume the 20 percent, and then the question becomes in my mind where does that happen, does that happen on a state, or regional, state, county or farm level.

I think based on what we understand about where resistance to the cyclodiene's emerged, that population spread through the corn belt, I think Dave is correct that it seem today start in a fairly localized area. So if, in fact, and there is a lot of if's in this,

but if, in fact, resistance to this product occurs in the same scenario, then I would think that if we do go forward with refugee that we need to have that on a farm basis, on a more local basis, than on a state level, certainly on a county level, perhaps. My preference would be to go probably on a farm basis.

DR. PORTIER: Dr. Neal.

DR. NEAL: I would also like to add that with our experience with rotation resistance in the western corn rootworm that that also started as a local phenomena in areas where crop rotation was greater than 80 percent of the control applied to western corn rootworm.

And that that resistance is then spread out of that area, so it is another exam will where the local level is extremely important.

DR. ANDOW: Do you have a sense as to how big local is in the case that you are referring to?

DR. NEAL: I really can't address how big the local is.

I guess I would refer you to Dave Onstad's model, for development of rotation resistance that is published in 2001.

DR. WHALON: Just a comment.

DR. PORTIER: Dr. Whalon.

DR. WHALON: For the record I think we ought to refer to the discussion that went on before and the lack of assurance essentially a baseline assurance that we knew what was happening in that rotation resistance phenomena before it was observed.

Whether a certain portion of the population was actually doing that all along is assertion now that it happens broadly.

DR. PORTIER: Dr. Hellmich.

DR. HELLMICH: With the refuge plan as it is right now, the refuge would be either contiguous with the edge of the field or inside? That's going to be the next question I know is going to be or within the field. I think the assumption is that refuge will be on an on farm basis.

What we're thinking about here having state caps or county caps, I think there may be some concern that growers won't be implementing refuge?

So I'm a little bit confused here, because the refuge as it is stated is on an on farm basis just like everybody suggested that it should be.

The question here is should there be caps, because I think that there is a little bit of mistrust that the growers will not follow the recommendations.

I just want to make that point clear.

DR. PORTIER: Any other comments on this question? New points.

DR. NEAL: I guess I would like to disagree with Rick on that particular point. It is not a question of trust of growers or lack of trust of growers.

It is a question of if you create the resistant monster, how does the percentage of acreage affect its spread, the percentage of acres

that is treated.

And if you have a situation where resistance would happen to develop or the individuals with that trait developed within an area, then if there is a lot of acreage in that area that is planted to the transgenic crop, then the resistance will be established more widely within that local area.

Whereas if you had less selection by having lower amounts within a particular area, then it would not establish as rapidly.

DR. PORTIER: So -- tough one to summarize, I guess, because I think there is a kernel in there that basically said again, conditioning on doing this.

There are parts of the panel that don't think you should -- that the science isn't there to do this. Conditioning on doing this, I think everyone concluded that if resistance is going to merge, it is going to happen at the local level, at the farm level.

And that if you are going put acreage

restrictions, there is -- there is a group of the panel that just doesn't think acreage restrictions are needed beyond the refuge restrictions.

But I think what people are telling you scientifically is that if you are going to puts acreage restrictions, then put them in the smallest, most practical sense, counties, or whatever, because there is no reason to go bigger than that scientifically, because the resistance is going to occur at the local farm level itself.

Is that sort of catching the point, if you are going to go with an interim plan?

DR. PORTIER: Any other comments? It will be much more detailed obviously in the report.

Okay, if we could move to question C please.

MS. ROSE: C states the panel is asked to comment on the adequacy of infield row strips and or immediately adjacent blocks to delay resistance during a three year period and whether one method or another is preferred.

DR. PORTIER: Dr. Hubbard.

DR. HUBBARD: Although 15 percent or approximately of the post mated preovipositional females do migrate some distance, we don't know how far, the majority of adult movement takes place within a cornfield and it has been categorized as trivial movement.

These data have led some to believe that strips may serve as a better refuge than blocks.

New data from Nebraska from 2002, notes that there is very little, if any, movement of females before mating.

Now the Onstad manuscript that came out this past year indicates that blocks may serve as better refuge than strips.

However, I think as we pointed out, bad data in, results in bad data out. I don't think that we have enough data. I don't think that that model has been validated, and I don't think we have enough data to favor strips or blocks at this time.

DR. PORTIER: Any other members of the panel who -- whether to asked to comment on this

or not have a different opinion?

Dr. Gould.

DR. GOULD: I would agree with you we don't have enough data. But to add to that, it should be noted that in the Onstad model, the infield strips are moved within the farm each year whereas the blocks are maintained fixed.

So if you want to understand that comparison on a science based, you have to recognize if he had moved those fields around so the farmer doesn't plant the refuge in the same place each year, he might have had a different result in that model.

DR. PORTIER: Dr. Caprio.

DR. CAPRIO: I'll also point out that there is a significant impact on the width of these infield strips that determined amount of isolation and impact of source sync dynamics and one of the things we have learned with cotton, the smaller, the more narrow the strips are, and that's pretty much what the Onstad models assumes, is they become much less effective.

And that can be -- there just isn't the data yet to know what would be an appropriate width.

DR. PORTIER: Any other comments?

Dr. Whalon.

DR. WHALON: Just a comment regarding the temporal delay or the phenological delay in the development of corn rootworm out of MON 863 versus the same hybrid without expressing the protein.

That is that I think this is an understudied and not well understood phenomena and that it could contribute significantly to intermating in the outcome of a refugesea strategy. And in that context, then, I think that the current resistance management plan as it is articulated is too restrictive. It may be actually advantageous to have a different hybrid.

Say, if you knew that the delay was 10 days, you planted 110 day corn with the MON 863 protein in it, you could plant 110 corn in the refugee and synchronize the beetles.

DR. PORTIER: Dr. Andow, and then Dr.

Gould.

DR. ANDOW: So the new point would be to invert the question a little bit and ask, is there any reason to exclude one or the other as being adequate even if we can't distinguish them at this point.

My perspective on that would be there is no reason to exclude one or the other.

DR. PORTIER: I would agree. In fact, I was going to make that point, Dr. Andow, and follow up by suggesting that because there is no reason to exclude, the interim management plan, to be conservative, should include aspects of both so that it can be evaluated and we can get the scientific information that helps us to decide at a later point which was more effective, if either are effective or needed, if you actually would move forward with this.

Dr. Gould and then Dr. Hubbard.

DR. GOULD: Dr. Onstad couldn't be here with us today. He sent me an e-mail, just to make sure that something about his model was understood. I

just want to get that on the record.

Onstad, et al., he says 2001 studies studied strips that were 6 to 12 rows wide. Rows more than .5 meters apart, the strips are not 9 to 18 meters from the center of the cornfield as the EPA question Number four indicates. This is the distance from each Bt corn strip to refuge rows.

DR. PORTIER: Dr. Hubbard.

DR. HUBBARD: My point is just to clarify the biology of the insect for the panel so they are not confused by Dr. Whalon's comment.

I think the delay in emergence of the females from the refuge or from the MON 863 corn is actually something that is going to favor the delay in resistance, because it gives time for the males from the refuge to move in to the MON 863 to mate and compete with resistant males.

DR. WHALON: My only comment relative to that is, I think that is a spatial question and a movement question. It relates to understanding what the distance per day of males are. And in essence you could move them out of the immediate

area beyond the MON corn if you waited too long.

So, I'm talking about trying to focus on synchrony, understanding movement well enough to do that.

DR. PORTIER: Dr. Caprio.

DR. CAPRIO: I think there is an important point with this asynchrony. If you did this sort of thing where you were planting refuges so they would come out synchronous with what are essentially susceptible individuals, coming out of the refuge.

What happens if you have a resistant individual that has normal development time? It has then emerged far ahead of that.

And again, I think we need to remember that we are not so much concerned with delay of susceptibles. We want to know what is happening with those resistant individuals, and we want to have our refuges prepared so that those individuals are emerging synchronous with resistant individuals or heterozygotes.

I think we need to bear that in mind and

not place too much emphasis on developmental delays of susceptible insects. DR. PORTIER: So if I can ask the panel again, getting back to the original question on C, is there any disagreement from the panel that there is not enough research in hand, right now, to make a decision between these two choices?

Does anyone disagree with that overall evaluation? We had a lot of discussion about what issues if we saw them, might change our mind on that, but currently I think that's the answer to the question.

Any new comments on C?

DR. HELLMICH: The only thing that I would want to say is giving a grower the option of doing one or the other may make it a more practical for them because then they could make a decision based on the equipment and their farming practices, and I think that's important.

DR. PORTIER: Yes, but also I don't want to lose my comment. And that is that it is important that the agency monitor this to some

degree to make sure that they get both aspects. Because we won't get the data we might need if we don't consider the comparison groups.

If we can move to question letter D.

MS. ROSE: The panel is requested to comment on the width of the in field strips as an example the agency is aware that at least 6 to 12 consecutive rows have been discussed in the Onstad, et al., paper.

DR. PORTIER: Before I go to the panel for comment on this question, we'll note the previous comment about the Onstad, et al., paper.

I will note that the panel has to some degree commented on this issue in the previous question. So now we will go and look at the comments on this question part D.

Dr. Caprio, why don't we begin with you, since you were giving us considerable detail on the strips a minute ago.

DR. CAPRIO: I guess, if I recall, the figure was -- female movement was approximately 10 meters per day.

DR. GOULD: Seventeen.

DR. CAPRIO: Under those conditions, any females that emerge out of a refuge this narrow will lay the majority of their eggs in transgenic corn.

I haven't run the data, I haven't run the numbers, but my gut feeling is that this is quite a narrow refuge and would be on the edge where you would speed up the rate of resistance evolution. Particularly compared to these out of field refuges.

DR. PORTIER: For clarify you are saying 6 to 12 consecutive rows is somewhat narrow --

DR. CAPRIO: Is on the narrow end of what I would consider just ad hoc, acceptable.

DR. PORTIER: Other lead presenters on this, Dr. Hubbard.

DR. HUBBARD: I don't believe that we have data to -- well, to verify a row width that is best that we should endorse.

One point of clarity in my own personal research is that, people have stated that my data

has indicated little, if any, movement across the row for larval movement.

That is the case for normal width rows, 30 inches or more, but we did have across the row movement narrow row corn which does exist in sugar beet areas in Minnesota. If we don't want larval movement across strips, you probably don't want it every other row, row for instance, especially in narrow row corn.

DR. PORTIER: Dr. Whalon.

DR. WHALON: Just two comments that I think might add to it, and that is that within, whatever the minimum is, whatever the minimum that one would prescribe, if we knew what that was, if we had the information to make that decision scientifically, I would say then that the second focus ought to be flexibility such that growers with different kinds of planting schemes pivots, as opposed to rectangular fields, as opposed to contour, et cetera would have the flexibility to fit that into their production system.

DR. PORTIER: Dr. Hellmich.

DR. HELLMICH: I have a comment. If you have a 12 row planter or you have three boxes on the outside that you are putting your refuge in, what you are going to have there is going to be 6 row strips alternating with 18 row strips.

Mike, my question for you is if you have these strips out there, some of those beetles are going to be ovipositing in those 6 row strips not just in the Bt strips.

And I don't know if your model takes that into consideration or not, that's one point. The other point I have made this point in a previous science advisory panel, is that we should be careful because we may be setting guidelines that would exclude some growers from using the technology.

For example, if you had a small -- a grower who has maybe only had a 6 row planter, he would only be able to do two boxes on the outside, and in that case, he would have four row strips.

And I think in some cases where equipment limits the -- there are equipment

limitations that smaller strips may be acceptable.

Otherwise, we get to the point where we are excluding some people from the technology and not others. And I don't think we want to make those recommendations. That's it.

DR. PORTIER: Dr. Gould.

DR. GOULD: I want to comment on this row, the thickness of whatever the strips. I don't think I agree. We don't have the science to know.

Since we're not dealing with a high dose that movement of larva in whatever -- narrow row corn probably doesn't manner so much.

The other thing we ought to consider in terms of plot sizes, is one seed that we should be dealing with. Actually, mixtures of seed in the seed bags there is no reason not to use seed mixes which might be an easier way to implement resistance management at this stage.

The science would indicate that that might be even better than anything else we're

talking about since we're talking about a moderate dose. I would like to say that the size could be anywhere from one seed to a field and that gives the farmer a lot of flexibility.

DR. PORTIER: Other comments? Dr. Caprio.

DR. CAPRIO: My concern just from the Onstad model, when he shows the difference between the out of field and in field strips, is one of the things you are doing is you are more approximating random oviposition across the field as you get these narrow in field strips, and you get source sync dynamics.

That evolves resistance more rapidly and the ultimate direction you would head for would be a seed mixture in that case. That would be perhaps the most rapid rate of resistance evolution if one can carry that comparison. And I may be carrying the Onstad model a little bit further than I should.

That's the direction I worry that a seed

mixture would go in.

DR. PORTIER: The other comments Dr. Gould.

DR. GOULD: I think that's very possible. I guess the reason I keep pushing these things is we don't have the science to know.

It could turn out is that a seed mixture would alleviate all of the selection pressure that we are worried about, because the beetles would indeed accumulate on the non Bt stuff. I think Bruce has some information on that, but we could certainly use a lot more. That might be a very effective strategy for delaying resistance.

DR. PORTIER: Have we covered the issue?

MS. ROSE: I appreciate the comments on seed mixtures, but the question wasn't about seed mixtures it was about the number of rows. I believe what I have heard is that 6 to 12 rows may be, from a science basis, too narrow. However, I haven't heard any information on what wouldn't be too narrow.

DR. ANDOW: I also heard very strongly

that there isn't enough information to really make that determination.

That from a theoretical perspective on -- and based on other in the check cotton system it might be. But there isn't sufficient information to make that point for this particular.

MS. ROSE: If that's the case then I guess I go back a question to the appropriateness of in field strips.

If we don't know how many strips, I'm not sure that we can recommend that as an option.

DR. PORTIER: I think on the previous question, the panel basically said we don't have enough information to tell you which of those two options to choose, in field strips or external plots.

Now we're telling you -- you are forcing us on the infield strips, and we're telling you we don't have enough information to tell you how wide those strips should be.

If you had asked the question how big should the external plot would be we probably

would have answered that question by saying, we don't have enough information to be able to answer that question for you.

Am I getting the census of the panel across here?

The argument that Dr. Gould was bringing in was that when you think about this, don't just think rows. Since we really don't have enough information, also consider seed mixtures if you are going to look at this. Which is the ultimate in terms of narrow necessary of rows, one seed apart check.

DR. PORTIER: Dr. Hubbard and Dr. Andersen.

DR. HUBBARD: A quick point, I also think Dr. Gould's comment is that a single row is adequate, single row strips, because larval movement doesn't matter.

DR. PORTIER: I don't think he said adequate I think he said that not enough science to justify the difference between one row and five rows. He is not saying it is adequate. Dr.

Andersen.

DR. ANDERSEN: Only if everyone is done.

I just want to say that with apologies for the mistake we made, we believe we can correct the comment from the e-mail from Onstad, that if the last word of that introductory paragraph was the word strips instead of field we think we were correct, so we apologize for the mistake.

DR. PORTIER: Ms. Rose, this is not the answer you wanted. Is it clear, are there some other issues?

DR. ANDERSEN: I think we're ready to go on.

DR. PORTIER: Let's move onto letter E.

MS. ROSE: Part E states please comment on EPA's conclusion that alternate hosts should not be considered and refuges should only consist of non Bt corn that are similar hybrids to the Bt corn.

DR. PORTIER: Dr. Hellmich.

DR. HELLMICH: I agree with that statement.

DR. PORTIER: Dr. Caprio.

DR. CAPRIO: I agree with that statement.

DR. PORTIER: Dr. Hubbard.

DR. HUBBARD: I agree with the statement. I also have more information that is applicable, I believe, as well.

Especially when you are getting towards stacked events with Round Up ready or herbicide resistance there is a number of alternate hosts that are out in the cornfield that larvae can develop to second or third instar on, and then move to the Round Up ready corn with the Bt gene. In the low dose event maybe it doesn't matter.

But anyway, the larvae, if you spray that herbicide resistance later on, after the larvae have already hatched, you are going to have a lot more adults coming out of that field than you may expect. We have data that we're currently working onto document that.

DR. PORTIER: Dr. Whalon.

DR. WHALON: I think I would just take

an attempt to summarize by saying that I believe that unlike the European corn bore, corn rootworms have limited alternative hosts, however alterations in the corn herbicide incorporation practices in particular, RoundUp Ready or something like that could change this whole perspective and it needs to be reviewed when that happens.

DR. PORTIER: Any other comments from the panel? Dr. Weiss.

DR. WEISS: As I read this question or this statement, I guess, I do not believe that alternative hosts need to be considered.

I believe that the refuge should consists of non Bt corn, but help me understand why the refuge has to be a similar hybrid to the Bt corn if the goal of the refuge is to produce susceptible males to mate. Why does it necessarily have to be a similar hybrid?

DR. PORTIER: Any comments from the panel? Dr. Whalon.

DR. WHALON: Actually, that's my point.

I think that by mixing days, you could cover the perspective that Dr. Caprio introduced and that we talked about somewhat yesterday, in that you could vary your strip or your block with different phenologically maturing corn, hopefully influencing the larvae.

Hence, you would have a longer emergence period and be able to cover a resistant and/or resistance on either end of the scale if there is an asynchrony that occurs.

DR. PORTIER: Dr. Weiss.

DR. WEISS: I agree with that Mark. If I look at the goal or the purpose of the refuge, it is to attract females, also that susceptible females to lay eggs for the next season to produce susceptible males to mate with the females.

So to me, the refuge really needs to serve a dual purpose. In one year, it needs to be an area where susceptible females can deposit eggs, and in the succeeding year then, it has to be a place where susceptible males are produced.

You may not want -- I guess where I'm

getting at -- you may not want the similar hybrid if you are trying to attract susceptible females to deposit eggs in that particular year. You follow me, Mark, is that -- I think we are on the same page.

DR. WHALON: I'm just saying there is a lot more flexibility here. Why limit the flexibility when you may be able to address resistant episodes that you can't anticipate a priority, so why not take the shotgun approach as opposed to narrowing your response in trying to promote the refugesea in potential mating that can occur from.

DR. PORTIER: Any other comments, Dr. Andow?

DR. ANDOW: Would one way to address that is that it is similar hybrids or similar agronomic practices or planted late. If the trouble with changing this kind of recommendation that it's similar, one has to also give some recommendations of how it could be dissimilar so that it is something that people can understand.

DR. PORTIER: Dr. Weiss.

DR. WEISS: Thank you, Mr. Chairman.

Dave, I haven't -- I guess I need to think it out.

When I'm looking at the refugee, I see it having to do that dual purpose. It has to attract susceptible females to deposit those eggs and then it has to be a place which are going to produce males the next year.

And we do know that if we have a field that tends to be later in phenology, it tends to attract, maybe not attract, but hold females for oviposition. We have used this strategy for many years to produce situations where we have high rootworm pressure the succeeding year.

So that's the other part. Then the other part, it has to be planted, it seems to me early enough because we know if we delay planting we tend to select for more females, but what we want to produce the next year is a lot of males.

We want to make sure we're planting it early to make sure we're producing enough males.

One year it has to be late to get the females to lay the eggs; the next year has to be planted early to make sure produce enough males.

If that's the goal, I don't see how it necessarily has to be of similar hybrid and similar agronomic to the Bt corn.

I don't know if my logic makes sense, but to me it does.

DR. PORTIER: If I can understand in my layman's terms here, what you are saying is it doesn't matter about alternate hosts or other corn whatsoever, as long as it satisfies the two necessities of a refuge as you have stated them it should be sufficient.

And do we have enough science behind us to say that there are no alternate hosts that would satisfy those two criteria?

DR. WEISS: I think for the western corn rootworm alternative hosts don't exist from a biological, practical standpoint. Northerns, I think, Bruce, correct me if I'm wrong, I think northerns have a little bit

broader, but again, I would think from a biological standpoint it would be relatively minimal. I can't comment on the Mexican and we stated yesterday that the southern has a huge host range.

DR. HUBBARD: Some northern corn rootworm adults will be coming off grassy areas around corn and that sort of thing. I have collected in adult corn rootworm off of -- trypscombactoloides (ph) that I did not infest this past summer.

DR. PORTIER: Dr. Andow.

DR. ANDOW: I believe Dr. Weiss' comments were -- pertained more to the second clause of this question.

DR. PORTIER: I brought it back to the first clause on purpose because his logic held for the first part as well.

DR. ANDOW: Thank you.

DR. PORTIER: That's why I challenged the question about are there alternative hosts. I think we have said that's less of a likelihood

that there are alternate hosts so that statement is probably stronger support from the Science Advisory Panel than the statement about it being a similar Bt hybrid. Dr. Caprio.

DR. CAPRIO: I would just say we talk about simplicity and lack of knowledge and so on.

In similar hybrids, you at least know what you are getting. If you take that wording out, there is all sorts of ways of growers that might be able to plant hybrid that are no ideal. We might be able to think of more ideal ways to do it.

But similar hybrid is a very easy way. It is easy for growers to understand. It works well.

I would just say in terms of simplicity, I think you get very complex if you start altering that similar hybrid question.

DR. PORTIER: Again, bringing it back to the science, are you saying there is a greater likelihood that you are going satisfy Dr. Weiss' two main criteria by using a similar Bt hybrid

than you would by using some other hybrid.

I don't know if the panel disagrees or agrees with that as a general rule.

I don't see any disagreements but at least that's we have got that out as part of the discussion.

DR. PORTIER: Any other comments on this question? No, shall we move onto letter F?

MS. ROSE: The panel is requested to comment on whether and if so under what conditions insecticides could about used in the refuge.

DR. PORTIER: Dr. Hubbard.

DR. HUBBARD: As stated previously, insecticides should not be used for adult beetle control whether intentional or fortuitous unless it is applied to both the refuge and transgenic areas equally.

Because of density dependent mortality beetle production for plants treated with tradition soil insecticides is sometimes higher than beetle production from untreated plants depending on the environmental conditions, the

product being used in their interactions, the adult emergence from soil insecticides targeting corn rootworm control ranges from 27 percent to as I stated more than one hundred percent of the nontreated chick.

Recent data from Nebraska, looking at some of the more recent seed treatments, indicate no differences in adult emergence between the untreated control and the seed treatments.

Fecundity is also an important issue, and variable data has been produced from traditional soil insecticides in the past. The data that is currently being collected for several modern seed -- data for this is currently being conducted from seed treatments that are under consideration for registration.

In areas where transgenic technology is most likely to be adapted, there is also likely to be a history of insecticide use for corn rootworm control.

Depending on the environmental conditions, yield loss from corn rootworm can be

extreme and growers will expect the option of applying insecticides.

I believe that soil insecticides and/or seed treatments labeled for and targeted toward corn rootworm control should be allowed.

DR. PORTIER: Dr. Whalon.

DR. WHALON: I think that there are several comments that have been made previously that are germane to this. I would just summarize my comments by saying that there is, I think, a tacit assumption particularly among the NCR 46 submission that we had in the public record, that seed and soil banning insecticide treatments will be necessary in the majority of the corn rootworm refuge acreage.

I don't think that I disagree with that. I can't speak for the panel yet, but I think generally that's probably -- general conclusion. Since these practices prevent economic injury in the refuge areas and yet produce up to 30 percent of population of corn rootworms seems logical and reasonable that that be allowed.

I think the greater question is what happens to other insecticides that are applied to either or both, because of economic injuries from other pests.

DR. PORTIER: Dr. Hellmich.

DR. HELLMICH: I agree with Dr. Hubbard in the NCR 46 panel that soil insecticides and seed treatments should be allowed. I agree with Mark, also that there may be some question about what some of the other aerial sprays are doing.

I'm sitting here trying to figure out what the strategy of the growers is going to be. In some areas in Nebraska as we well know, they spray for adults.

If they have the Bt option, I just wondered if they will abandon that altogether. Because if they have to spray both Bt and non Bt if they are going to be doing that, they might as well just spray and forget about using the Bts.

I'm just curious how the growers will respond to this, but I agree with all the statements that have been said, is the bottom

line.

DR. PORTIER: Dr. Caprio.

DR. CAPRIO: I'll just reiterate what I have said before.

Those sprays would reduce the effective size of that refuge that just needs to be kept in mind. It seems like growers would need to put on those insecticides.

DR. HELLMICH: Talking about soil insecticides, right?

DR. PORTIER: Do you agree that --

DR. CAPRIO: I agree --

DR. PORTIER: -- you spray both the refuge and the Bt crop. Do you agree with Dr. Hubbard's comment that if you are going to spray, you spray both?

DR. CAPRIO: If you are going --

DR. PORTIER: If you are going to use an insecticide.

DR. HELLMICH: Aerial?

DR. CAPRIO: I don't know -- as far as soil insecticide, I would suggest that that only

be used on the refuge, but that then you -- that goes back to the comments about refuge size, and we didn't agree on that.

SPEAKER: We agree on that. I think he was talking, though, about subsequent treatments for other pests.

DR. WEISS: Mr. Chairman, I think I need a little clarification here. I think you and the panel have lost me.

Bruce, did you say that growers should be able to use an insecticide at planting in the refuge?

DR. HUBBARD: Yes.

DR. WEISS: But you did not say they could use an aerial application for adult control.

DR. HUBBARD: If they use anything that is going to be kill adults it should be treated equally to the refuge and the MON 863.

But Dr. Andow had a very important point on this in terming of the timing of that, could affect refuge. I had not thought of that before he mentioned it.

DR. WEISS: I just want to make sure I was on the same page. If I look at this and allow me to kind of explain what I'm what I'm thinking, if we look at this in a growing season, to me a producer if we went with an on farm refuge, we would actually have two refuges perhaps.

We would have the attractant refuge planted to attract females and hold females for oviposition in the late summer and we would have other refuge being used to produce males that growing season.

If the production refuge, if -- and I guess this is more of a question, in the production refuge component that was being used to produce planted early produce a high population of males, if that was treated with an insecticide, do we know enough of how that would reduce male population compared to female population.

Has that study been done?

DR. PORTIER: Dr. Hubbard.

DR. HUBBARD: Actually, yes, the 1991 the document.

DR. WEISS: I'm trying to -- I thought that work had been done but I couldn't recall how they had done it.

My point is I think producers should not have to suffer an economic loss. So in the production refuge that is going to be used to produce males, if that was scouted, and above the treatment threshold then growers should be able to use a soil insecticide to protect that block or that refuge. My question is more biological, then if they do that, will that impact the ability of that refuge to produce males, and that's the question.

DR. PORTIER: Dr. Hubbard.

DR. HUBBARD: According to Sutter and Hale 1991, Journal of Economic, volume 84 1905 to 1912 the mate survivors of females ranged from 22 to 46 percent of the adults that were produced. In other words, more males were produced from the insecticide than females.

DR. WEISS: With that, then, I think it would work out fairly well?

Now the other component problem or the other side of the question is should growers be able to use aerial application in the refuge that they are using to attract and hold females to lay eggs for the succeeding males the next year.

And again, if they were using that based on a threshold, occasionally growers will have to treat for silk clipping by adult rootworms but if they are going after another insect perhaps corn bores an arthropod, spider mites, then I think they should have to spray the refuge and the Bt treated corn.

DR. WHALON: Just to comment on that. I wonder is -- this is a question to the panel really. As I think about this, this subsequent spray targeting alternate pests, if you are going to -- the question of recruiting females for eggs into the subsequent refuge is an important one -- but if you are going to take advantage of redundant mortality, it might, this is an alternative tactic, it might be wise to actually treat the MON corn and not the refugee I can't.

DR. PORTIER: Do we have disagreement or uncertainty? Dr. Andow.

DR. ANDOW: I'm not sure. I think there is general agreement about the use of the soil insecticides. But I wanted to -- currently, the soil insecticides are -- have the survival rates that as Dr. Hubbard suggested.

But if a new one comes along that has a high efficacy, I think this issue would need to be revisited again.

And that's the only supplement that I wanted to make to the soil insecticide side of the question.

DR. PORTIER: Okay. Any other points on this question, Dr. Gould.

DR. GOULD: Are you asking for points on the question, not F? Before we leave this entire question I would like to make a comment.

DR. PORTIER: I want to finish up F before we -- are we finished with F? I'm not going to try to summarize what Dr. Weiss said. It is beyond my ability here. Dr. Hubbard.

DR. HUBBARD: I think he is just stating some of the way corn rootworm entomologists do their research by recruiting adults to lay eggs in certain areas. He is implying that the refuge should be done that way.

Unfortunately, I think it is more complicated than would be acceptable to the growers of the or the EPA. I think it should be just a straight refuge for this years's crop and not worry about next years's crop yet.

But that there is going to be some egg laying everywhere just not as much as there would be if you delayed your planting.

DR. WHALON: Consider this idea of redundant killing. If you are producing resistant females in the MON 863 Bt plants, and you are going to, because of an economic injury being breached by another pest, would it not be an advantage to get redundant killing on the putative resistant individuals generated by the transgenic plant and not the refuge.

DR. PORTIER: Can this be handled in our

report as additional comments above and beyond the general comment about ground based insecticides and some other potential things to consider in looking at how to manage the refuge?

Do we have general agreement on that? We don't have to all agree on these individual points.

No disagreement with that? Any additional comments on part F?

DR. PORTIER: Before we leave the question, Dr. Gould had a general comment he wanted to make.

DR. GOULD: I have been thinking about this science based policy. And I just want to make a comment to EPA. You are looking for our advice our advice goes beyond helping the farmers in a small way and in the United States.

The policy decisions that you make, I have had a lot of experience with this, go beyond the borders of the United States. Some countries too small and too poor to make their own scientific risk assessments just accept everything

you say and 20 percent whatever it is, is what they are going to use and they are going to assume that you do the Science.

Other country that have enough money or power to look into this, look to the United States and say we're just trying to export this technology. Our science is shoddy and they don't want to accept our grain.

So I just would reiterate that you really need to have science based policy. And I think the EPA has done a great job compared to a lot of other agencies in doing this. I hope you will continue in your path.

DR. PORTIER: I'm going to show pity on the audience and the panel. I don't believe we can finish these questions before we're going start passing out from hypoglycemia.

I believe we're going to have to take a break at this point and go to lunch. Before we do that, I regret that I will not be back after lunch. I have a 3:30 flight that I must catch.

So I make my closing comments now and

say that as always, this has been an exhilarating meeting for me. I have learned a lot of new things, and had some very useful discussion that I'll take back into my own work.

I think we have answered some serious questions for EPA. I want to thank their staff for being so patient with me and the panel for being so patient with my ignorance on this issue.

I'm going to go beyond my earlier point about the openness of this process, because I think there is another point to be made here, and that is I have seen tremendous cooperation between the academic community, the corporate community, and the EPA on this issue.

To bring the important issues to the forefront for discussion.

Again, that's a very refreshing exciting way in which to manage this type of issue for both the agency and the government as a whole.

I'm quite pleased to have seen that. After lunch, I believe Dr. Roberts will take over as Chairing the session. Again, I want to thank

you.

Dr. Lewis, do you have any comments?

DR. LEWIS: Two brief remarks. First of all, for the panel members, during lunch I would appreciate if you could bring lap tops to the break room.

Your laps will be configured for the upcoming work group, report writing process, so we have some we have contractors in the work room that would help to configure your lap tops, leave them there, they will work on them while you are having lunch, they will be secure. Just meet us there in the next few minutes.

To Dr. Porter, again, thank you also for serving as our Chair for the past three days. We really appreciate your insight, and working with the panel in terms of directing them to respond to the questions and for the work in that area.

DR. PORTIER: Thank you, very much. Dr. Andersen.

DR. ANDERSEN: We want to give our thanks too. You have done an excellent job of

moving us along. We really appreciate it, for your insight that you have given it is always nice to have lots of perspectives and you have really contributed.

You will be missed this afternoon, but we also do recognize that Dr. Roberts will undoubtedly do a good job for us with this.

DR. PORTIER: I'm sure the entire panel will breathe a sigh of relief. Dr. Roberts knows a little bit more of this than I do.

Thank you all very much. We'll see you after lunch, in one hour. The time now is 1 o'clock, so I guess 2 o'clock.

(Thereupon, a luncheon recess was taken.)

MS. ROSE: There is actually only one question for monitoring and we ask: please comment on the agencies conclusions regarding refinements to Monsanto's Resistance Monitoring Program.

In your response, please consider the following factors. How should corn rootworm resistance be monitored, the value of developing

resistant colonies of corn rootworm to determine the mechanism and genetics of resistance, insect rearing for corn rootworm species, and whether one colony in more than one laboratory should be established.

DR. ROBERTS: Dr. Hubbard, could you lead off our discussion on this subject?

DR. HUBBARD: Monitoring a baseline susceptibility over time is important. Unfortunately, this is not an easy task complicating factors with such basis elements as even obtaining a lethal dose to a product that is not that highly toxic make this matter not an easy thing to do.

Other complicating factors including rearing the insects that require diapause. Some populations of the northern corn rootworm may require two diapause periods.

Artificial diets are poor and difficult to control, mold from soil insect -- and there are many other complicating factors I'm not an expert in doing these sort of tests.

It is possible, I understand, to measure susceptibility to neonate corn root larvae to Cry 3Bb1 using the dose a response curve. This is likely the only method that will be available to document whether susceptibility is changing over time.

Other possible triggers for suspected resistance, I'm not sure whether these are good triggers or not, but these are ones that have been mentioned in this panel, could be tunneling of a certain damage for instance, Dr. Andow mentioned tunneling as a possible trigger, Mike Weiss mentioned percentage of males that come off of these as another possible trigger. I'm not sure whether any of these would work, but after some sort of a trigger, a dose response curve is likely going to be needed to be done.

One other alternative to a dose response curve might be possible if researchers had access to other events that had different concentrations of Cry 3Bb1. For instance, MON 862 likely produced the endotoxin in higher levels. MON 853

produced the toxin in lower levels, I believe. MON 854, I'm not sure what level that produced, but it did protect the plant in -- at levels similar to soil insecticides in my study.

An interesting note if we turn to page 108 of the Monsanto's IRM plant, we see some data that I generated documenting the production of more than three times as many adults from MON 854 as the infested check without insecticides. MON 854, produced an average of 46 beetles per plot or per emergence cage, whereas the infested check was something of 13 or so.

So there are events with differing levels of Cry 3Bb1, and I'm not sure if researchers would be able to get access to those, but I understand that that might be another way, other than a dose response curve. And I defer to the panel because I'm not really an expert on these sorts of measurements.

Sensitivity is another key issue. No method is likely to be sensitive enough to be useful in finding resistance early on.

This is partly because it is low dose event and partly because damage by this insect is underground, partly because environmental factors play such a huge role in the damage done by these particular insects, and partly because above ground symptoms of damage such as lodging are often caused by events other than corn rootworm feeding.

If you have you heavy winds and lots of moisture you are going to have lost corn whether you had rootworm or not.

Developing a resistant colony does have value, and is worthwhile to pursue, but has not been pursued to date in the public sector. Wade French, from Brooking, South Dakota, plans on doing so.

The nondiapausing colony of the western corn rootworm that is available has been a lab rat for more than 200 generations. These insects do cause field damage but they are poor fliers and likely represent only a small fraction of the genes in the wild western corn rootworm populations.

However, developing a resistant colony within a reasonable time frame, is likely only to be successful with a nondiapausing strain. And so it would be good to intergress wild genes from differing populations into a nondiapausing colony before attempting to go develop a resistant -- a colony resistant to Cry 3Bb1.

Currently, I'm a ware of one colony of the northern corn rootworm. That is in Brooking, South Dakota, I'm not sure if Wade French has a colony or not. This is a diapausing colony. I'm not aware of colonies of Mexican corn rootworm.

And so, developing resistant colonies from these species is likely to be impossible.

That's all I have.

DR. ROBERTS: Thank you, and just for the sake of clarity, when you mean developing a dust response curve, you mean direct treatment under laboratory conditions that sort of thing.

DR. HUBBARD: Yes.

DR. PORTIER: Dr. Andow, what are your thoughts about approaches to monitoring.

DR. ANDOW: On the several questions here.

I think one approach to monitoring first of all, it is clear with this particular species and these particular species this particular event that monitoring is a challenge.

So handling individuals is probably not going to be a very effective way of monitoring. However, monitoring doesn't necessarily have to get tied to -- monitoring just has to be -- to give you sufficient information to take some actions.

And so, that sort of rather than focusing on whether it gets you just a piece of information you feel you might need in order to determine if you can get information that is useful to take actions, I think that's important to focus on that side.

And for this particular species, it would be very useful, I think, to think of a tiered the approach to monitoring. Where you would be doing something that has that is

relatively on the spectrum of things, it is relatively easier to do, but has a slightly I higher error rate in terms of giving you the information.

So that if you get a positive response, then you would follow it up with something else, rather than thinking that that was all you do.

And so some of these suggestion that we were developing earlier, this idea of doing root ratings -- looking not at root ratings but looking for root tunneling could be in that category, because we already know that there are certain things that could complicate it.

At the same time, we could be taking information and whether or not those complicating factors are involved.

So for example if you are just looking for root tip damage, you might instead of doing the normal root ratings at the time of anthesis or later, you might go in during the late oral stage and look at roots at that point, after the first instars have done their damage rather than waiting

for the second and third instar damage to accumulate. There are ways to sort of approach this in another way.

Now, another possible approach, and this would be a more intensive approach, would be to try to develop a survival test. And since we know that corn rootworm survival is quite variable from place to place and soil to soil, maybe it would be useful to standardize the soils and standardize the location.

Like green house studies with a particular type standard soil and see just how variable is corn rootworm survival, susceptible population of survival, under fairly constant controlled conditions. If it turns out that it is not that variable, then it may be possible to collect adults from the field, get them to lay eggs out on charcoal and test those eggs on a standardized plant assay in the green house.

So all of these are research areas. But I think that one needs to develop something that is a lot easier than dose response assays in the

field or even discriminating dose assays.

Those assays at the individual level you can't get the numbers up high enough to expect that you are going to be able to monitor over any extensive areas or ranges.

Even the ones I'm talking about are still not going to be as extensive as one might want. However, I think that there are -- and I would also guess that if the NCR 46 community were to sort of decide, instead of thinking just about toxicity, what kind of evidence would give us some indication that resistance was developing and sort of go in those sorts of things rather than try to sort of, say at the beginning what is the definitive piece that would prove that we have resistance.

You can always go in afterwards and do that, but to sort of look at a tiered approach to try to develop some earlier tools, I think that would be very helpful.

So that's on the monitoring question.

Should the value of developing resisting

colonies? I think that would be very valuable. Work that has been done on or helicoverpa armigera of the Bt cotton is a low dose type event, has proven that mass selection in the laboratory has developed -- has given some very useful results.

And so that should be something that is pursued it may be that that is going to be the fastest way we end up with a resistant individual that we can start working with. I would be strongly encouraging that.

The insect rearing, this is a much longer term project. It certainly is a useful thing to be thinking about because of the problems in rearing northerns compared to westerns.

In terms of how high a priority, I would probably be pushing more towards thinking okay, if northerns were getting resistant, what types of things would I expect to see that would give a little signal of that. And sort of, more push it into what are the characteristics we can monitor rather than necessarily try to go all out with a rearing effort in the case of the northerns.

But in the -- where you have it in Brookings, you may as well try to do some selections on it if you can.

Then the last point about more than one colony, I think that there is some limitations as to what we can really expect is feasible with northerns. But certainly with westerns since there are multiple colonies already, there is no reason to say that it shouldn't happen in more than one colony.

DR. ROBERTS: Is that it?

DR. ANDOW: Yes.

DR. PORTIER: Dr. Caprio, what are your thoughts about monitoring strategies and approaches.

DR. CAPRIO: First, I would like to agree that the Monsanto plan needs considerable refinement.

I agree pretty much with what David said, that we need to find some easier method to monitor, and I'll just throw it out as part of a brain storm as I sat here thinking, that one of

the other things you might expect with some forms of resistance would be an alteration of this delay period. If you could look for earlier emerging adults, that might be a sign that there is some sort of resistance.

I think there is value in developing resistant colonies. We also have to be careful that -- that is no guaranty that that is the only mechanism that is out there, or that that is what will evolve in the field if there is multiple mechanisms and certainly multiple attempts to select for resistance might give us idea. That's pretty much my comments.

DR. ROBERTS: Are there other panel member that would like to offer thoughts on monitoring strategies? Is there anything with which other panel members disagree?
Is the silence because everyone agrees with what was said, or maybe they just don't have an opinion. Is there any disagreement with the comments that were made, or voiced during the discussion? DR. ROBERTS: Dr.

Neal.

DR. NEAL: I would like to add that monitoring for resistance with this pest is going to be extremely difficult and is going to be very difficult to determine that resistance is developing before it actually shows itself full blown.

DR. ROBERTS: I think Dr. Hubbard made that point as well in his comments, that it is going to be tough to see this early.

Dr. Hellmich.

DR. HELLMICH: Just one comment. Bruce's suggestion of using other events somehow to be incorporated into the monitoring, that's something we actually considered early on with the corn bore.

I understand at that time there was a problem because that event would also have to be registered in order for it to be used in that capacity.

That limits that option, I think.

DR. ANDOW: Couldn't it be done under

the EUP type approach, because we wouldn't be talking about huge acreages.

DR. HELLMICH: Sharlene, Do you remember this conversation we had about five or six years ago where we considered doing something like that?

DR. ANDERSEN: I might be brain dead on that one, but you can depending on the acreage, you can do things and certain other aspects about it. You can do things less than 10 acres, as long as the protein is not going into the food supply, unless you have a temporary tolerance or permanent tolerance. So there are some things that way.

Larger -- in experimental use permits, it is the same aspect. You have to make sure it is not going into the food or feed supplies in unapproved variety. With that caveat, you could do it. I guess I thought maybe Bruce was talking more about greenhouse studies. And I thought that was -- so it was different and I thought a very interesting idea.

DR. HUBBARD: I was referring to

greenhouse studies, that's how I would conduct those.

DR. PORTIER: Dose response things that you talked?

DR. HUBBARD: She is referring to the varying levels of Cry 3Bb expression found in different events that have been tested over time.

And I'm aware of at least one event that has higher expression and there may be other event that have even much higher expression. I'm not sure if that's Cry 3Bb or what.

DR. PORTIER: Any other comments on this response to this question?

Ms. Rose, is the panel's response reasonably clear.

MS. ROSE: Yes.

DR. PORTIER: Let's go ahead and take the last question, which is on mitigation remediation action -- remedial action.

MS. ROSE: Part A states, the panel is requested to discuss an appropriate method of determining suspected and confirmed resistance for

corn rootworm, including recommendations as to how suspected resistance or unexpected damage may be identified.

DR. ROBERTS: Dr. Hellmich, you are the lead discussant on both A and B. Could you start us off on A.

DR. HELLMICH: I have a number of things here. Some of it overlaps with what some previous speakers have said.

Certainly with suspected damage or suspected resistance, the first sign for the grower is going to be plant lodging.

I think that some of the steps that should be taken, then, is first of all you have to confirm whether or not the grower did indeed plant MON 863 seed and you have to rule out that there wasn't other insects responsible for the damage. In the same vein, weather conditions that may cause lodging, and to rule all those out.

Then you have to confirm that indeed the plants are expressed in the protein. One other thing I want to add some of the things that Bruce

suggested, is that I could imagine a situation if there was excessive weediness and then the herbicides were an applied you could have had first instars maybe get started on some of the fox tails or whatever that is out there, and then go over to the -- move over to the plants.

In some cases you may get unexpected levels of damage. So that would be something that they would want to at least consider as a possibility.

Of course, after all those things are ruled out, there is protein expression, then you have to take it to the next step. How do you confirm resistance.

Unfortunately, Blair Sigfried was in the audience, but he has left now I talked to him a little bit about this. The first step right now as I would see it would be to conduct a standard diet bioassay, try to do a diagnostic dose.

But Blair, who is the authority on this, admits it is going to be very, very difficult to come up with a test for this. Because the events aren't very effective, so trying to see if they're

becoming a little bit more -- a little less effective with this population is going to be very difficult normally, at least with the high dose, we would try to do a standard diet bioassay. We look at the 95 percent confidence intervals. If it was outside of that, then you would indeed think that may have resistance.

And then we come back to maybe some of the ideas similar to what Dave and Bruce were saying about using plants maybe in greenhouses to see if you get more node feeding, especially for the early instars, that may be some way to confirm resistance.

When you have this unexpected lodging more than likely when they go out there to look at this, you're going to be looking at adults, the third instars, the earlier instars won't be there anymore.

I was thinking that at the time if there were third instars, you could possibly test those. But to do that you would have to have LC 50's determined for the later instars. That hasn't

been done, but more than likely, you are going to be encountering an adults emerging from those. You have to test -- test their children.

When it comes to unexpected damage, as I was saying before, I think you have to look at this sort of two different levels, and one is the practical level, the grower level, and as I mentioned the excessive lodging would be what they would be looking for.

Certainly, they would be calling Monsanto in these cases to see what was -- what the problem was.

From a lab perspective, again, we -- again, we keep coming back to this idea of first instar tunneling whether or not that can be detected, and if that could be sort of a sign that there is a problem.

I think that should be pursued, but with understanding that it may be very difficult, because the second and third larval damage more or less covers that up. And it may be difficult to interpret looking at stage in this or looking at

the sampling at a time when -- before you get second instars as Dave was mentioning before, may be a pretty good idea.

Mike mention the idea looking at the sex ratios. I think that a lot of discussion we had -- we suggest that this would not be very accurate. It would meet so many environmental conditions, planting times, whatnot. But that would probably not be a very reliable method to use.

Then there is always the problem with, and this is the problem we always have, with monitoring and unexpected damage is that presumably, before you get to the field failure, there could be some signs of resistance developing that can't be detected.

Unfortunately, unless they use some of the monitoring, I think they are going to have to fall back to the monitoring, and see if they can't fine tune those, so that they can detect it before you get to the field level.

Unfortunately, I feel that in most cases, it is going to be the growers coming across

the unexpected lodging. It is probably going to be the first thing that is going to be visible and that the earlier detections with the monitoring, in many cases is not going to be extensive enough, or practical enough, or sensitive enough to detect resistance before it is problematic. That's all I have to say for A.

DR. ROBERTS: Thank you, let's go ahead complete our comments on A and then move to B.

Dr. Whalon: I think that Monsanto's interim IRM resistance detection as it is described is inadequate for full registration.

I think -- I think that because the appropriate methods for determining suspected resistance aren't there, and the ability to confirm resistance is very difficult, the current plan would only detect field failure or nearly so. And in that sense, would be too late.

The IRM plan would be defeated in a sense. It depends on how wide spread it is. So this is a situation I don't see as being Monsanto's situation. I think it is a situation

associated with where we are at on the science, and where we are at on understanding the biology and the toxicology of this event in corn rootworm.

I think in response to that, there needs to be a concerted, mounted effort on the part of the public sector corn growers and the registrant to get this information. So that this product will live for a while in the field.

I think it's necessary to develop those protocols and identify the means whereby such detections could be made and all the comments in the previous section on monitoring apply here.

I recognize that this is a considerable technical challenge that presents and that there are a lot of significant, very significant aspects to overcome. Particularly, with conventional bio assays.

The comments regarding the development of a resistance resistant strain, I agree with, I think that you could get a resistant strain with one approach or another. May not be the one that occurs in the field. This is always a risky

approach but something is better than nothing, and will inform at least for that mechanism.

I broke out the second part in terms of recommendations on how to -- suspected resistance or unexpected damage may be identified. I think that the current rating systems both one to six and the zero to three are probably not systems that will effectively identify early stages of resistance.

And that presents --

DR. ROBERTS: Maybe we ought to go ahead and finish one and come back around to do two. This is a response to B?

DR. WHALON: It is the latter part of A where it says including recommendations as to how to -- suspected resistance or unexpected damage may be identified.

DR. ROBERTS: I'm sorry, continue please.

DR. WHALON: One of the things that would be really good, ideally, is that if you could identify these events before adult emergence

such that you could initiate a medication strategy.

So, that kind of thinking that way might dictate how a detection system were developed if it could be developed.

In essence, what the registrant has proposed is to move ahead operationally with a system that practically probably wouldn't be able to detect.

I think there is also some adoption problems as we talked to growers the other day. Some of these strategies are done by other competing hybrid seed companies. How interested would they be in following through on monitoring for Monsanto or this events.

I think there is some practical issues too, to deal with.

DR. ROBERTS: Dr. Hubbard, do you have anything to add?

DR. HUBBARD: I agree with most of the comments.

I agree with Dr. Hellmich, in that it is

likely to be the growers that see something and unfortunately when they see something, it is probably already crop failure.

But if they do see some unexpected lodging with low levels of damage from MON 863 it is possible they could see this relatively early on under certain weather conditions, if there is moisture and high winds, you will get more lodging and you will get more lodging in feeding corn -- in corn that has rootworm feeding than that which has not.

A Mosanto representative could then watch those roots, evaluate for feeding damage, and I think under the concurrent -- they could take a look at that whole field. I think that they actually might be able to, if there is a lot of damage, in more than a node, or half a node of damage right there and you have some nonBt plants of the area and they have a similar amount of damage, then I would say that's -- you could use root ratings to detect this fairly early on.

So I disagree slightly with Dr. Whalon on

that point. If you have the refuge available that is damaged similarly, because usually even insecticide treated refuge the MON 863 has less damage than the insecticide. One other point is you probably should distinguish that these larvae actually, western corn rootworm or northern corn rootworm, versus southern corn rootworm.

Because it may be that southern corn rootworm is not on the label and so the actual larvae causing the damage should be collected.

That is all I have.

DR. ROBERTS: Other panel members, would any of you like to comment on A?

Dr. Caprio.

DR. CAPRIO: Just one thought as you were talking, if you want to compare with a non Bt strain probably we ought to think about that same hybrid type situation that that might play into that.

In a broader issue, not really to harp on this, but we're talking about an awful lot of

problems with both monitoring and resistance detection and so on.

And one of the reasons people were willing to accept smaller refuges was that we could with corn bore, people could do a relatively good job monitoring. And one can see a lot of these problems that -- maybe that ought to be a consideration until being more conservative in terms of how much refuge we might recommend.

DR. ROBERTS: Dr. Andow.

DR. ANDOW: I'm -- I support that, but the points that I would like to raise is in terms of the proposed definition for confirmed resistance, which I don't know if this has been modified very much at this point, but on the Monsanto interim plan on page 16 I'm going to be referring to that section, and so basically, there are two different branches.

One, is you either use a discriminating dose assay or this series of test that they list. As we heard from Rick earlier, the discriminating dose assay may take a long time to development, so

what we're really looking at is the other list -- is the functional definition of resistance for a long time.

And that functional definition of resistance has two components of which both have to be met.

And I'm go to go review this a little bit because I'm going to propose how they might be different. One is that the resistant population or the putative resistant population that you have has to have an LC 50 that exceeds the upper 95 percent confidence interval of the mean historical LC 50 for the susceptible population.

And then the second point is that in addition, over half of the plants that are exposed to this population in a laboratory condition have to have one or more root nodes destroyed. That's sorts of the present definition.

Now it seems to me that the first piece actually -- it actually seems to me that it's not clear why you need both.

Because if you have a populations that

is destroying one or more root nodes that is pretty resistant and you really need to have the other test to confirm that, so that's one point that I would be raising.

The second point is the LC 50 test it sort of depends on the slope of those LC 50 lines as to whether or not you may be missing actual resistance or not. Because if the 95 percent confidence interval is going to be large which given the difficulty in doing these tests it is go to go be large, then to have something way above the LC 50, if the slopes are relatively steep, you may end up with concentrations, populations that wouldn't pass the LC 50 test, but would still be able to damage the corn.

It seems like that first condition may be too strict.

It seems to me that something based on the damage to the root nodes maybe sufficient or even if one were to develop an survival assay, it is pretty clear that survival of courtrooms on a susceptible variety without insecticides is higher

than the survival of corn rootworms on the Bt variety.

You get variance associated with each of these. But then if the test population tests within the confidence interval of the susceptible population on the susceptible variety then one should consider that to be resistant also. It seems that would be an alternative way of confirming resistance.

In other words it is not that it is different from the Bt control but it is not statistically different from the control line on the control plan.

And if it's not statistically different from the control line on the control plant, I don't see how you can say that that is not resistant. It seems there are other approaches toward defining this that are sort of or type definitions rather than and type definitions.

That is one point that I wanted to make.

DR. ROBERTS: I was going to ask if panel members had questions for you on that point,

or wanted to comment on that.

DR. WHALON: Just a general observation. I think in the LC 50 concentration test because of the noise of the study and the low efficacy of this compound on the target insect, that the likelihood of being able to detect three or for fold level that could be related to resistance is fairly low.

DR. ROBERTS: Anybody else?

DR. HUBBARD: I agree with both comments.

DR. ROBERTS: Dr. Andow did you have another comment you wanted to make as well?

DR. ANDOW: Sort of a general comment in terms of how to frame how to look for things here. It seems like I said under the monitoring dealing with these -- for this event dealing with the beetles individually, is just not going to cut it.

So I think we need to be thinking about all of this as population issues. Sampling populations, we're testing populations so all of the frameworks could be built at the population

level.

And then moving into the question of -- there was a question raised in the corn bore issue as to how to sample and where to sample. That wasn't really brought up here. But in terms of how to do a suspected and confirmed resistance, I'm going to bring it up in that context.

In previous discussions, I have proposed that there is sort of two extreme ways that resistance may arise. The frequency may creep up gradually over a large region, or it may occur at spikes in a particular area, and how you target monitoring in those different approaches would be quite different.

In this case, it seems to me that the local source -- you know we've been saying resistance should arise locally, that the spiking of resistance is probably going to be the thing we have to be looking at more closely.

Now when you have that kind of a situation, there is no way you are going to be

able to monitor everywhere for resistance because it is too big of an area, and there is to many people. So you do have to rely to some extent on the growers there.

And so I don't disagree with Rick's assessment that the idea that you look for lodging is a very come important component for the resistance. But the other way to do it, another supplement to that would be to identify those regions with high adoption. That's sort of at the county level rather than again, the local level and maybe just take the top 10 or 20 of them and suggest that you try too do a little bit more intensive monitoring associated with those.

Because -- in this case because of the nature of the event, it is likely that you will see the responses more associated with those high concentration areas.

So that would be another thing to look at. And then it might be possible to get a couple years head start on field failures if the

monitoring program is developed well.

DR. ROBERTS: Thank you, Dr. Andow. Are there other comments in response to this question. Yes, Dr. Neal.

DR. NEAL: I would like to point out that a lot of this discussion of MON 863 is specific to MON 863 and would not necessarily apply to a high dose plant transgenic directed at corn rootworm.

If it were a high dose, then that would make the monitoring for resistance much easier, because then you could look at numbers of beetles emerging from fields.

The other point that I would like to make with regards to monitoring is that polygenic resistance should be expected to appear in that some of the previous suggestions we took up another question in other questions directed toward measurements of growth, development, and fecundity of naive corn rootworms and corn rootworms selected by being reared on the MON 863 that doing those kinds of comparisons should give

a good indication of the polygenic resistant component.

DR. ROBERTS: Other comments in response to this question. Is there any disagreement among panel members on any of the comments that have been made so far, or are we pretty much in agreement?

Silence is assent?

DR. ROBERTS: Ms. Rose, was that response reasonably clear do you have a follow up?

MS. ROSE: I was hoping the panel could elaborate a little bit on what you mean by unexpected lodging. I'm not sure if you would expect some level of lodging since we're not dealing with a high dose.

How would a farmer or grower be able to go out and say, I wouldn't expect this level of lodging.

DR. ROBERTS: Dr. Hubbard, do you want to tackle that one?

DR. HUBBARD: I think they should expect no lodging unless the whole region has lodging due

to a high moisture, high wind event.

DR. ROBERTS: Anybody else? Dr. Hellmich.

DR. HELLMICH: That kind of means that low levels, low amount of lodging that is not due to weather, which a grower -- of course it could be confused with corn bore lodging too. Could it?

No? Okay.

DR. ROBERTS: Let the record indicate Dr. Hubbard made a gesture that indicated he wasn't sure whether that was true.

DR. HUBBARD: I think that you can discriminate. I think entomologists can discriminate between rootworm and European corn bore lodging. Farmers probably should be able to.

DR. ANDOW: Is it possible that wireworms would cause lodging.

DR. PORTIER: Question from Dr. Andow, or Dr. Hubbard I guess.

DR. ANDOW: In terms of what to expect and what not to expect?

DR. ROBERTS: Do you want to respond,

Dr. Hubbard?

DR. HUBBARD: No, I'll defer to Dr. Weiss.

DR. ROBERTS: Dr. Weiss, respond.

DR. WEISS: Thank you Dr. Hubbard. I would say that wireworms usually do not cause lodging. Injury is early in the season, you will get stunting of plants and mortality, but not lodging.

DR. ROBERTS: Have we clarified that for you?

MS. ROSE: Yes.

DR. ROBERTS: Anything else on this one before we get to the last question? I think we're there. Last question.

MS. ROSE: Please discuss whether root ratings are an appropriate indicator of suspected resistance. If so, how could a typical farmer use root ratings to identify suspected resistance.

DR. ROBERTS: Dr. Hellmich.

DR. HELLMICH: Maybe.

DR. ROBERTS: Okay, anybody else?

DR. HELLMICH: I think root ratings for most your growers won't be very practical. I think that again, this gets into the discussion we were having before, about whether or not a trained scientist could tell whether or not there was unexpected damage with the nodes being eaten.

And I think that there may be some sort of education of growers so that the more dedicated growers who are really interested in this, could indeed find it. But I would think that would be the rare grower. Most of them won't be out there digging roots trying to find out what is going on.

But if I do think it is important that the crop consultants and those people who normally would be digging roots, that they are trained to assess if there is any kinds of unexpected root pruning that -- DR. ROBERTS: Dr. Whalebone, what is your position on root ratings?

DR. WHALEBONE: The root ratings I think are an inappropriate indicator of suspected resistance.

However, I believe that root ratings may

be able to be adapted or refined in such a way that they could be. I think, in terms of adoption I an agree with the previous comments. It is unlikely that growers are going to do it however consultants may be able to.

These people that are out looking at cornfields all the time, like a couple of the scientists on this panel, may be able to use that. The real challenge really is to get an uniform modified system into the hands of the growers in an appropriate way or in the hands of people who are looking at corn in an appropriate way to be able to detect such a low level effect.

DR. ROBERTS: Dr. Hubbard.

DR. HUBBARD: I agree with the comments of the previous two speakers, that he typical grower is not going to use root ratings.

Lodging is more appropriate. I think root ratings are one indicator for resistance that can be used by those educated to do so, such as crop consultants.

DR. ROBERTS: Other panel members? Dr.

Hellmich, did you want to make a follow up point.

DR. HELLMICH: I would like to put a plug in for the Iowa State, no injury scale as probably being a little bit better to detecting differences, than the others ones. I think that there may, like some of the scales we used to use for corn bore leave ratings, there may be modifications of that that could make even a little bit better. I don't know you would have to talk with John Tollefson and see if there would be something.

I personally believe that the zero to three scale is -- would be more logical and would be a better root rating scale than the one to six scale.

DR. ROBERTS: Are there other opinions? Dr. Hubbard.

DR. HUBBARD: I strongly concur.

DR. ROBERTS: Anyone else on the panel have an opinion on root ratings? Dr. Neal.

DR. NEAL: I would like to post a question to the panel that we have a situation

where we have a low dose plant.

So that if highly resistant individuals did develop within that field, then those individuals might be a relatively small proportion of that population. And would the average root rating mask the heterogeneity of the population or the fact that he had a mixed population.

DR. ROBERTS: Dr. Hubbard.

DR. HUBBARD: Absolutely. One insect is not going to cause much damage. Dr. Andow's suggestion -- no Dr. Caprio's suggestion that adult emergence that is not delayed is probably the best -- the best indicator that I have heard from this whole panel.

But there aren't that many adult emergence traps out in farmers's fields.

DR. ROBERTS: Dr. Andow.

DR. ANDOW: I guess it seems like this is oriented at local field failure in which case then hopefully there would be mitigation that could be locally applied.

But in terms of -- because this is

pretty severe damage that we would be talking about, and the only way a farmer is going to be involved is if there is lodging through an extensive area of their farm or their field and if they notice that, then they are probably going to call and get some people in, and to investigate why it is lodged in which case then there will be several people available to pull up roots.

And if, in fact, this new Iowa root rating scale it is a two or a three, it is kinds of a no brainer; there is so much damage to that root that you know it is root worms.

DR. ROBERTS: Any other comments on root ratings?

Okay. Let me then give the panel the opportunity to make some comments if there have been some issues or matters related to insect resistance management, some points that you think need to be made but weren't necessarily covered in the questions that were posed to the panel yet are nonetheless are important and valuable for the panel to convey to the agency, this is the

opportunity to do that.

We have gone through all the questions posed to the panel by the agency. I wanted to give the panel members the opportunity to make some follow up comments. Dr. Hellmich.

DR. HELLMICH: I think we have all learned a lot from this panel. I think one of the main points is that we all came in here sort of thinking in this high dose refuge paradigm.

We're finding out that what we have here is much different, that sometimes the questions are much different there has been a shift in paradigm and that we really are in sort of unknown territory. That's one comment.

Another comment is, I think it is unfortunate that some experts weren't able to be here to -- because it would have provided a lot of valuable input.

The other comment is that obviously, there is a lot of science that -- there are a lot of gaps in the information. In that and that we should have a mechanism for figuring out how to

fill those gaps.

We talked a little bit at lunch. There is a history of NC 205 working with industry, working with the EPA and then the 46 has also has done that.

I would like to think that -- I'm going to challenge the panel to identify some of the research, some of the test that need to be done so that we could in some capacity perhaps, Bruce, since he is a member of 46 go back to 46 and say these are the questions we need to address, so that the research can be focused.

I know from experience that there is a lot of research that gets done and not all the researchers are privy to the conversations that are going on, and consequently, maybe the data, not all the data is collected just right.

Maybe some experiments are being done that don't need to be done. So this dialog needs to be ongoing.

I think Fred may be interested in participating in this. I would like to thank the

EPA for giving us the opportunity for doing this.

And I -- one other thing I was thing I was going to say is that I think some panel I think some panel members have the idea that sometimes the technology is ahead of the science, and that we're having a panel now and that with a little bit of forethought, that perhaps the discussions that we're having right here now, they should have happened three or four years ago.

I don't know if there is a mechanism to -- for that to occur. But if there would be a way to have the appropriate discussions in science discussed in a more timely way so that the experiments can be done in a more timely way, that would be useful.

DR. ROBERTS: Dr. Gould did you want to make a comment?

DR. GOULD: Yes, I would. I would like to respond to some of the things that Rick brought up. I also would like to thank the EPA for having this open forum, again, it is not done in all agencies. I think it is a healthy way of doing

risk work.

I did push for science based risk assessment before commercialization, and I guess one of the things that came back at lunch and also from other people was, okay Gould, what do we need before we go out there.

So to be more specific. So I did come up with a list here. I can read it to you or --

DR. ROBERTS: Please do so, so it will be in the record.

DR. GOULD: What is the scientific information we need before commercialization, really. What is the selection intensity on -- so we can have a real resistance management program. What is the selection intensity on corn rootworm larvae for MON 863 in different regions, soils, moisture, and at different densities.

Two, what is the selection intensity on corn rootworm males and on females separately from MON 863.

Three, what is the selection on progeny through maternal effects if there is a carry over

that you wouldn't see in the first place.

Four, what is the impact of using whole fields versus rows within fields as refuges and what is that effect on population dynamics on the percent refuge beetles mating with resistant beetles from the Bt fields.

Five, how would use of a seed mix impact selection intensity.

Six, are some of the surviving larvae on MON 863 more genetically tolerant of the Bt toxin than the general population.

Seven, what could we learn from a quantitative genetic model.

And finally eight, is male female movement different in different regions.

I'm sure that there is more in that than list, but these are the things we ought to know before we go out there to commercialize.

DR. ROBERTS: Let me follow up and ask you to what extent are these general applied beyond this particular MON 863, but are things that you would look for, for other potential

products?

DR. GOULD: I think we would need this for any product. But these tests many of them have to be done with 863 for the MON 863 registration. And we have to ask about selection intensity on the other events. But understanding the movement and things like that --

DR. ROBERTS: The extent to which these could be generalized and become, sort of, principals of the application. I guess that was what I was looking for.

DR. GOULD: For a high dose situation these would not be as applicable.

DR. ROBERTS: We might -- I'm just wondering if you want to frame this as these are important for moderate dose corn rootworm resistant products.

Dr. GOULD: Yes.

DR. ROBERTS: To make it clear this doesn't apply only for this particular situation.

DR. GOULD: Yes.

But it applies to moderate dose.

DR. ROBERTS: Yes, Dr. Whalebone.

DR. WHALEBONE: A couple of observations, one is that the benefit side of this technology is strong. I'm sure the agency is going to consider the benefit risks in terms of resistance. It is also worth noting that transgenics are in a fish bowl. This same standard that we're applying to transgenic products are not applied to other conventional chemistries.

From a public policy perspective, this is probably wise given what the situation is and focus on GMO's in general.

Finally, this paradigm shift that Rick was addressing earlier, and that we have talked about for a couple days now, is not just associated with the area of GMO's and transgenics it is also part of what we're facing in some of the pesticide alternatives that come to us through biopesticides.

These paradigm shifts come and science has to adapt so does the grower community. How we

move ahead to facilitate that adaptation is challenging. So, in this instance, classical approaches may not apply. I particularly like some of Dave Andow's comments and other comments that related to that. That we need, as scientists, to adapt as well. We may have to develop techniques and strategies that are out of the box.

DR. ROBERTS: Yes, Dr. Andow.

DR. ANDOW: I guess, in terms of what research is really important, I might prioritize the list a little differently and pick out two of the ones that Fred said that I would particularly highlight.

This is the selection intensity. He had a bunch of them associated with fitness differentials, associated with -- and those are really critical. I think the occurrence, first present occurrence of resistance, if it is there or not, is really critical.

If it is there a lot of what we're talking about is just irrelevant, and so it is

really important.

I also think that if it is not there at high levels, then the monitoring issues really need to get tackled that we need to have monitoring methods worked out, and we also need a clear mitigation strategy. Right now it's not so clear what the mitigation strategy is. To have a full plan, there has to be an initial plan to move in. There needs to be a monitoring strategy and a mitigation strategy.

And I have to say that -- to that's what is needed. That's going to be very important to see that. So, I would put those as priorities and deemphasize some of the other things. But that's just my opinion.

DR. ROBERTS: Thank you, any other comments. Dr. Hubbard.

DR. HUBBARD: I would like to just relay a few bullet points from the NCR 46, May 30, 2001, in research needs.

One is to quantify the relative fitness of rootworm individuals that survive on transgenic

corn versus nontransgenic corn.

Evaluate IRM options other than a refuge especially if an event is not classified as high dose.

Examine the impacts of refuge configuration including seed mixtures on development of resistance and likely hood of farmer adoption.

I think those are some of the points that NCR 46 brought forward. They brought forward other components, but those three seem germane to our discussions.

DR. ROBERTS: Dr. Gould.

DR. GOULD: Just to finish up with my comments on these research initiatives.

It was said that maybe this would take 100 years to get done, and I don't think so. I think that all the things on the list if you prioritize them the way Dave did some of the NC recommendations could be done in two years if the funds were made available.

DR. ROBERTS: Last call for comments

among panel members.

Ms. Rose, did you have any follow-up questions that you wanted to pose to the panel before we close this session.

MS. ROSE: The only follow up question I would have thought of is research we need, so very good.

DR. ROBERTS: We have anticipated that and have some suggestions for you, terrific.

Dr. Andow.

DR. ANDOW: I would like to acknowledge Monaco in that they spent a lot of effort putting together this interim plan and they circulated it quite widely. I think without to the focus of some of the EPA's questions today, a lot of these issues didn't -- and didn't occur to me and didn't occur to a lot of people to bring up earlier.

So I think that the whole process has been very valuable. But I did want to acknowledge that they had been circulating this to many people, and getting input.

DR. ROBERTS: Dr. Gould.

DR. GOULD: I do want to ask a question to EPA because I have been told as time has gone on here that we haven't seen the research that has been done. There is more research done than we were given.

I'm assuming that we're up-to-date. If that is not the case, it makes our process more difficult.

DR. ANDERSEN: I think you have everything we have.

What we are anticipating from what we have heard from Monaco is that they are just finishing up some reports from some of these places where we have provided you with preliminary data and that's what we have looked at.

So we will be getting that data, and obviously looking at it in light of the comments we have heard today and what we will see in the report.

DR. GOULD: Finally, I would like to say this is a list, but I hope it will be okay with the people here to embellish these with a little

bit more detail in the report.

DR. ANDERSEN: Detail sounds good to us.

DR. ROBERTS: That will be fine Dr. Gould.

Anything else, before we close the session?

If not, I would like to thank all of the panel members for their hard work in taking a look at these questions and issues posed by the agency.

This is very important stuff and we really appreciate the comments and valuable discussion we have had during this meeting.

The panel will prepare a report from this meeting, which is the minutes from the meeting. I would like to ask the panel members to -- in order to plan for the preparation of those minutes to meet in the break room immediately following the close of this section so we can discuss how we're going to organize our write up.

I would also like to thank the public commentors for their input into this session. It

is always very important for the panel to receive different views and different perspectives from these issues.

Of course, I would like to thank Dr. Porter, who isn't here who did the bulk of the work in Chairing this sessions and made it very easy for me to step in at the last second and finish it off.

Lastly, I would like to thank the SAP staff for putting the meeting together. There is a lot of hard work that goes into putting a panel together, getting them here, and supporting all of that. They do an excellent job. I would like for thank them for that.

Let me give our Designated Federal Official, Mr. Paul Lewis, to make any comments, if he would like, before we close the session.

DR. LEWIS: Thank you Dr. Roberts, for filling in for Dr. Porter serving as our Chair this afternoon.

Again, express my appreciation to SAP members for all your hard work the past few days

and the upcoming work we have together writing a report that serves as our minutes based on discussions we had the past few days.

As Dr. Roberts mentioned, if we can meet afterwards, we can go over this afternoon our structure follow developing work, in terms of writing our report.

And also, finally, for the public for staying involved, in the course of this week, the people that are here thanks for participating and playing an active role in our scientific peer review process.

Thank you.

DR. ROBERTS Dr. Andersen.

DR. ANDERSEN: Again, thank you. You have heard lots of thanks, ours too from the agency's perspective, it does have the SAP group.

So in case you don't exactly understand, they are a bit you autonomous from the Office of Pesticide Program. On behalf of the office, we really appreciate your time and effort. There have been some excellent suggestions that will

apply to us, I think, on the overall about PIPs, as well as these specific products so we really appreciate some of the thoughtful ideas we have heard last few days.

DR. ROBERTS: Thank you Dr. Andersen, if there is no other business, this session of the FIFRA Scientific Advisory Panel is closed.

(Thereupon, the meeting adjourned at 3:20 p.m.)

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I, Frances M. Freeman, Stenotype Reporter, do hereby certify that the foregoing proceedings were reported by me in stenotypy, transcribed under my direction and are a verbatim record of the proceedings had.

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