FIFRA SCIENTIFIC ADVISORY PANEL (SAP)

OPEN MEETING

SCIENTIFIC ISSUES ASSOCIATED WITH THE

AGENCY'S PROPOSED ACTION UNDER FIFRA 6(b)

NOTICE OF INTENT TO CANCEL CARBOFURAN

U.S. ENVIRONMENTAL PROTECTION AGENCY

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U.S. ENVIRONMENTAL PROTECTION AGENCY

FIFRA SCIENTIFIC ADVISORY PANEL

OPEN MEETING

FEBRUARY 6, 2008

MS. MATTEN: Good morning, I think we'll start Day Four. My name is Charlene Matten. I'm the designated Federal official for this scientific advisory panel meeting on scientific issues associated with the Agency's proposed action under FIFRA B6 Notice of Intent to Cancel Carbofuran and this is our last scheduled day, and we will resume momentarily on the charge questions related to the human health risk assessment issues associated with carbofuran, and just as a side comment, just for the sake of just a tiny bit of humor as I was doing the Stair master last night it's somewhat like being at the last twenty-five minutes of a very long sweaty spend and we're at the last five minutes so thank you for all of your endurance.

I think that this day will be the shortest of the ones that we've had so far and I appreciate the panel's participation and eagerness to provide the Agency with as fruitful comments as they have and I hope we will be able to continue that today. Thank you very much

DR. HEERINGA: Well with that humble picture in mind. I'm Steve Herringa the Chair of the FIFRA Science Advisory Panel. I am a statistician from the University of Michigan, Institute for Social Research and my specialty is doing applied statistics in population based research. I'd like the other members of the Panel to introduce themselves to you, I think there are a few new people in the audience.

DR. CHAMBERS: I'm Jan Chambers from the College of Veterinary Medicine at Mississippi State University and I'm a pesticide toxicologist, I am a member of the permanent panel.

DR. PORTIER: I'm Ken Portier, a statistician from the American Cancer Society, National Home Office in Atlanta and I'm a member of the permanent panel.

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

DR. CLARKE: I'm Larry Clarke, I'm the Assistant Director of the USDA's National Wildlife Research Center and my expertise is in wildlife ecology, sensory biology and wildlife diseases.

DR. DELORME: Good morning, I'm Peter Delorme, I am currently Acting Director General of the Environmental Assessment Director of the Class Management Regulatory Agency in Canada. My expertise is in environmental risk assessment methods, aquatic toxicology and environmental.

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

DR. HILL: I'm Elwood Hill, I'm wildlife toxicologist expertise is organic phosphorous carbonate and mercury toxicology.

DR. MCCARTY: John McCarty, I'm a professor of biology at the University of Nebraska at Omaha, I'm an ecologist specializing in the ecology of birds.

DR. MONTGOMERY: I'm Cheryl Montgomery, I'm the principal and owner of Montgomery and Associates, I am chemist and my area of expertise is risk assessment.

DR. SAMPLE: I'm Brad Sample, I am a consultant with CM2M Hill, my background is in wildlife toxicology and ecological risk assessment.

DR. STINCHCOMB: Audra Stinchcomb, I'm associate professor of ecology and pharmacy at the University of Kentucky and my area is absorption.

DR. REED: Nu-may Ruby Reed, toxicology, California Environmental Protection Agency. I do pesticide risk assessment.

DR. MACDONALD: I'm Peter Macdonald, I'm professor of mathematics and statistics at McMaster University in Canada and I have general expertise in applied statistics.

DR. LU: Good morning, Alex Lu from Rollins School of Public Health at Emory, my research interest is using biomarkers to assess human exposure and the health effect.

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

DR. HATTIS: Dale Hattis, Clarke University, mechanistic modeling and uncertainty of variability.

DR. EDLER: Lutz Edler, German Cancer Research Center in the Biostatistics department with various sources of physical data analysis and risk assessment.

DR. BUNGE: Annette Bunge, from the

Department of Chemical Engineering at Colorado School of Mines, my expertise is in dermal absorption and risk assessment.

DR. BRIMIJOIN: Steve Brimijoin, Department of Pharmacology and Clinic, my interest is in cholinesterase biology and toxicology and entomology.

DR. BAILEY: Ted Bailey, Iowa State University, my interests are in applied statistics and design and analysis of experiments.

DR. HEERINGA: Gary, if you'd like to introduce yourself.

DR. ISOM: Good morning I'm Gary Isom, Professor of Toxicology, Perdue University, my expertise is in neurotoxicology but my interests run further than that.

DR. HEERINGA: For those of you who weren't here yesterday, Dr. Iceman I think is actually I think in Lafayette, Indiana at this point and is delayed in getting back from the West Coast due to the weather so he's at home joining us by phone.

Well, welcome back everybody and panel members, I want to again reiterate Dr. Matten's statement of appreciation, not only to panel members but all of the participants. This has been a long

process, a very informative one, a tremendous amount of information brought forward. I look forward to the discussion this morning of the charge questions on human health issues, just a few minor administrative issues. As I indicated yesterday afternoon, the period of public comment is closed, however any written comments submitted by the public, before the close of the proceedings today, can be considered by the panel as part of their deliberation. We have received two items yesterday afternoon and I checked with the relevant panel members, that they've had a chance to review those to acknowledge that information. Those were generally responses to questions of clarification that had been raised earlier.

In addition, I know there are a few additional comments on the ecological risk evaluation component of this. Mr. Montgomery I think what I will do is to wait until we're done with the human health and revisit it as there may be a few others. We will have a wrap up before we break up today that will go through any remaining questions and issues and I think that if would be appropriate.

At this point in time I'd like to turn to the EPA scientific staff for the discussion of the human health risk charge questions and Dr. Reaves or Jeff

will be, Dr. Lowit who will be reading the charge questions into the record. I guess you have an initial presentation summary Jack Housenger, good morning.

DR. HOUSENGER: Yes, I just wanted to say that we're...we just have a few points of clarification, we want to go back and summarize our position, some of the comments that we've heard both from the registrant and the public we want to be able to address. Most of the comments fit in with our initial recommendations but there is something on the new exposure data from the AHETF that we'd like to address just to be on the record.

DR. HEERINGA: Panel members, you should have a copy I believe of the slides from that last evening so put a colored banner over the top, probably if you run clarifications in summary to the charge questions. Thank you.

DR. HOUSENGR: So Dr. Reaves will go through the presentation, I have a few words to say on the human studies review board issue and then Jeff Dawson will talk about AHETF data.

DR. REAVES: Okay, good morning, I just have a few clarification statements and some summary points concerning our charge questions this morning. It shouldn't take too long. First, the acute oral just

as a reminder, the Agency is relying on the brain cholinesterase data from the PND11 pups as a planned departure with a BMDL10 of .03 milligrams per kilogram and the uncertainty factors that we've been using intra species, of course the 10X for human variability.

For intra species the Agency is applying a 10X for extrapolation of animal to human and unlike FMC's request on Wednesday to rely on the human data the Agency is agreeing with the Human Studies Review Board, their conclusions in 2006, that the oral human study is scientifically deficient so the Agency is not relying on this study to inform the uncertainty factor for carbofuran.

For charge questions 1A and B then the red blood cell data set, the red blood cell data from the second FMC CCA study are unreliable. The Agency has not used this information and this is on the basis of the protocol in measuring acetylcholinesterase in the number of DNR's that were present in this study and were highlighted on Tuesday in our presentation. However, in the EPA studies we don't have low dose information in the PND 11 and PND 17 pups so we've missed the low end of the dose response curve for red blood cell.

DR. HATTIS: What was the number of

those, what proportion of the data points had to be excluded because of the...

DR. REAVES: The DNRs you mean...it varied from ten percent up to sixty percent in controls so it was in all treated groups and in control groups.

DR. HATTIS: Thank you.

DR. HEERINGA: Panel members could the rest of us hold our question until the presentation is done, I would appreciate that.

DR. REAVES: Okay, and in this study too each time they had to re-evaluate or rerun the assay it took approximately twelve minutes so when you re-analyze the sample up to three or four times, you're adding time and possibility for reactivation of the enzyme and this is why the Agency has not relied on the red blood cell data, that the brain data set is a more robust data set.

We have information from the low dose range to the high dose so we have a good spread of data. We've included both FMC CCA studies including the EPA studies for our BMD analysis. There is good concordance between the EPA and the FMC studies for brain as I showed on Tuesday when we put all the data together, there is good concordance and again just the BMDL .03 is based on the brain PND 11 pups.

Finally, for the FQPA factor just as a reminder the 10X mandated as a margin of safety and only with reliable data can we move away from that 10X. The Agency, because of the RBC sensitivity in the pups and because we don't have that data, the Agency feels that we must retain part of that 10X factor and so we've looked at the data to see how we can derive a refinement of that FQPA factor.

So for charge questions 1C and D, like I said there was remaining uncertainty than the lack of red blood cell data especially at the low end of the dose response curve for pups.

Our data derived approach is consistent with the international communities specifically with the 2005 IPCS guidance on chemical specific adjustment factors. This guidance is for the use of equally effective doses for example the BMD 10 or the BMD 50 and we went through that comparison on Tuesday and as Dr. Setzer explained the BMD 50 there is less uncertainty because we have data around this dose. Unlike the example presented by FMC on Wednesday by Dr. Silkin which was to compare effect at the same dose. And so the Agency has relied on the BMD 50 for data derivation of the FQPA factor instead of the BMD 10 because of the lack of red blood cell data at the low

end of the dose response curve and therefore uncertainty around that estimate.

As far as the Agency's cholinesterase policy use of the red blood cell cholinesterase data as a surrogate for peripheral nervous system is our policy and single chemical assessments is standard practice for us to evaluate the relative sensitivity of these compartments, the red blood cell versus the brain and that red blood cell cholinesterase has provided as the basis of point of departure for end points for some of the other carbamates for example, aldicarb and methomyl so we do consider both compartments in our assessments.

So that's all I have as far as the oral endpoint. The dermal, I'd like to make some clarifications. FMC brought up some points on Wednesday regarding the seven day and twenty one day dermal studies. The molar activity assessment that was done in the twenty one day and the FOB I should say was done prior to the last exposure on day twenty one. So approximately eighteen hours after the last exposure the motor assessment and FOB was assessed so based on the profile for the carbamates we would not expect motor activity changes at this time point. A rationale is not provided why a motor activity assessment would have been performed eighteen hours after exposure.

However, that's what the study report indicates. In the seven day study blood samples were taken approximately, or it says within thirty minutes of rinsing of test substance. That was taken directly from the study report. For the twenty one day the report says samples were taken immediately following the removal of test substance. That's as far as I can tell, we don't have exact timing of when the samples were taken so that's just for clarification and the DER for the twenty one day will be updated with this information.

So the seven day and the twenty one day dermal studies, the cholinesterase methodology was the same as that used in the second CCA study from FMC. There was considerable measurement problems with especially the red blood cell data. We went back and looked at the twenty one day study. There were DNRs in that data as well. Each dose group had at least one to three DNRs with two to three re-analysis of the sample, so again reactivation of the enzyme and so the Agency feels due to a study design and the protocol issue with the cholinesterase methodology that the study is not reliable for use in our risk assessment.

Another point FMC brought up was that we have other twenty one day studies without the other

information, the time course, the recovery type information, however as you can see here there are several studies in which we have called the study unacceptable based on the lack of time course and recovery information for formetanate back in 1999, we got a study without this type of information. We deeded that unacceptable and did not use that risk assessment in 2000. Then time course information was submitted and the Agency then used this in conjunction with the twenty one day study and for the timing of the cholinesterase measurements.

Again for aldicarb we had a study. It was deemed unacceptable until a one day with time course information was provided. Same for oxymil, we had pilot studies with this type of information and on carbaryl we have a lot more data including pharmacokonetic data.

FMC further stated on Wednesday that the dermal studies are supportive of using the twenty one day rat dermal study, this was from slide number nine of the worker presentation. However, the EPA strongly disagrees with this conclusion and I'll say again, that the human study, we've not relied on the human study as point of departure or for informing uncertainty factor that we think the...because of the issues around the

twenty one day study should not be used in risk assessment. However, we did go back to the human study in order to clarify our point and why we disagree with FMCs suggestion. If we look at the rat dermal study there was brain cholinesterase about ten percent at fifty milligrams per kilogram.

We would then add on a hundred uncertainty factor for a derivation of .5 milligrams per kilogram. However, if you look at the human dermal study, there is red blood cell cholinesterase in addition at .5 the same level and this was in two subjects and of course we don't have brain to compare from the human studies so it's another point that the red blood cell is important consideration in regulation and either with a 10X or a thirty X uncertainty factor that brings you to a much lower dose for regulation so if we consider the human study it would not be protective of human health and we feel that based on the rat dermal study alone is not sufficient for use in regulation.

I should further state that there were severe symptoms at two milligrams per kilogram, typical of carbonate toxicity including lightheadedness, weakness, vomiting, muscular cramps, abnormal balance and atropine had to be administered up to three times in one subject so this was severe clinical science and

again we agree with the Human Studies Review Board in 2006 that the study was unethical and scientifically deficient that although it was informative it should not be relied upon for point of departure or for informing uncertain factors in risk assessment.

DR. HOUSENGR: I just want to try to explain the procedure with the HSRB, it's kind of uncharted here we've like Elizabeth said, we've already gone to the HSRB with the dermal studies. Initially we had said that we wanted to use them to establish a point of departure and reduce the uncertainty factor. However after they reviewed it they found them both scientifically and deficient and unethical and recommended that we not use these studies. They did say they were informative.

We ended up adopting the Board's advice, we haven't used these studies and we reviewed the FMC twenty one day dermal rat study and we think that it alone has enough deficiencies that it doesn't warrant our justification for using it. If the Board, the panel agrees with our determination we think we're done.

We don't have to consider the human study. If the Board wants to...is a little bit uneasy about adopting our recommendations on the twenty one day

dermal and thinks it is of use which is the twenty one day dermal rat, we would ask that they also consider the human study, the dermal study that was found scientifically deficient and unethical.

If the panel does that then we're required to go back to the Human Studies Review Board and we're prepared to do that if it's needed. There's a Board meeting in April and then we would have to go through a number of other procedures including issuing a Federal Register Notice for Comment and issuing our final decision.

So if there's...I'm not sure that I captured all the things that are tied up in that, but that's the gist of it. We think that we've made the case on not accepting the rat dermal study, however in order to be protective we feel pretty strongly that we shouldn't accept that and if the Board...if the Panel doesn't agree with our conclusions then we want to bring up the human study. So at this time I'm going to turn it over to Jack Dawson who's going to talk about some newly submitted exposure studies for the egg handlers exposure task force.

DR. DAWSON: Good morning, Jeff Dawson, a scientist in the health effects division. Just a couple quick words on the worker exposure data. I

realize it's not part of the specific charge to the Panel but it might help provide some context to the discussion around the dermal end points this morning.

First of all there was a lot of commentary the last few days around the use of the egg handler exposure task force data, that's the acronym AHETF, and the risk assessment for carbofuran, there are actually...actually several more scenarios where we're in agreement with the registrant on the exposure side of the risk calculation so the real discussions is only around a couple of the specific scenarios and there are major use scenarios for carbofuran.

Another issue is that in 2007 a year ago many of you on this Panel provided a review to us about worker exposure methods and one of the issues that we touched on there was study design issues and how do you populate a data base of exposure estimates which is we're still struggling through and that that's one of the major reasons for the next bullet I'll talk about so and in that SAP we talked a lot with the egg handler task force about how to develop data to represent specific tasks in agriculture associated with the application of pesticides.

So with a couple that are in specific, there were comments were heard about yesterday it's closed

mixing loading and application by pilots for those public scenarios we're still expecting more data from the task force and we're still in the process of analyzing them and addressing some of the specific issues that were raised a year ago at the SAP so that's why we've not implemented fully the use of those data.

The other thing was in the some of the presentations that were heard, and in the submission or the comments that we have from the registrant they've chosen to use a different exposure statistic than we may ultimately use and our risk assessment is based on a combination of the use of medians and geometric means and the values that you saw from the registrant were geometric means so there's...that's one of the reasons for the differences in the risk estimates.

Also the numbers that we're using from our data base include the devices that you saw demonstrated by the registrant and the public comments but one thing I heard in the presentation was that carbofuran is actually sold also in California with different devices that may have a little bit more exposure associated with them. In the data that we're using actually incorporates those types of exposures as well.

But the bottom line for all this is if we use the data that we talked about in the comments where we

use our exposure estimates, the basic risk picture still looks the same for carbofuran. Risks are still a concern regardless of which piece of exposure estimates you base the risk calculations on.

DR. HEERINGA: Thank you very much Jeff. Dr. Reaves, Dr. Isom didn't hear the initial presentations. I think you used the term DNR, would you just lay out your version of that acronym.

DR. REAVES: Yes, DNR stands for Does Not Replicate, this surrounds the acceptance criteria for the red blood samples that were run in duplicate so the duplicate must replicate within eighty percent of the first sample.

DR. HEERINGA: So Gary just to be clear it was a replication issue on the actual assays or measurements not a do not resuscitate. Okay questions from the panel, that's Dr. Bunge.

DR. BUNGE: I'll read my joint...Annette Bunge. My question relates to the values that reported just now in your presentation on the human dermal studies. I'm looking at the HSRB report from May of 2006. In that report it says neither subject dosed with one or two milligrams per kilogram experienced any symptoms. A dose of four milligrams per kilogram resulted in symptoms which you list on your slide as

four two. Is the report incorrect?

DR. REAVES: There was two studies, with a Phase A and Phase B and there was a subject at two milligrams per kilogram that showed symptoms and required atropine.

DR. BUNGE: Either the report that we have from the HSRB is incorrect or you're incorrect and I don't know which.

DR. LICCIONE: Let me give you a clarification on the study. This is John Liccione from HEB. There was actually several studies, the 1977 study consisted of three phases, A, B and C and they look at high temperature, high humidity and that is the results from the one of the phases of the study where there was also exercise involved. There was a latter study that 1978 as well and in that one there was no symptoms of '04, but here you know there's some mild exercise involved, a little higher temperature and humidity.

DR. BUNGE: The data that I'm reporting, or reading from the report is from the second study.

DR. LICCIONE: Phase B 1977.

DR. BUNGE: 1978. The Phase B earlier study didn't see any symptoms if I recall.

DR. LICCIONE: No, there was one

where...

DR. BUNGE: There was one subject...

DR. LICCIONE: That's the 1978 study where you are referring to the 1978 but there was also the 1977 study which had three phases, an A, B and C and then one that was .5 where there was cholinesterase inhibition and it was simply recorded at two milligrams per kilogram per day.

I know it's confusing they did...they first did a series, the 1977 study was three phases and they looked at temperature, humidity as well as some mild exercise for five minutes. The 1978 study also looked at the another set of study and in that case they did see symptoms of roughly about four.

DR. BUNGE: The red blood cell cholinesterase inhibition data that are quoted at the top bullet from the first study or the second study?

DR. LICCIONE: From that first study, Phase B, the 1977 study.

DR. BUNGE: If you'll notice up on the screen now Dr. Reaves has put a similar slide of each of the phases of the two studies done.

DR. LICCIONE: The first three studies listed there are Phase A, B and C of the 1977 studies and that captures the conditions of temperature and

humidity. The last column is the human study 1978, okay, the last row you also see .5 milligrams per kilogram per day. It is nowhere in the slide except there's a word, you are correct, that four milligrams per kilogram per day. There was actually a little mild nausea in that first subject at .5 but the other dose was I think one in adults in between that where they didn't have that.

DR. BUNGE: Well, in the red blood cell cholinesterase inhibition according to the HSRB report at the half milligram per kilogram per day was quite unreliable because one subject had only a seven percent, I don't think that was supposed to be significant and the other one had... the twenty two percent.

DR. LICCIONE: Twenty two percent...right. and that's one of the deficiencies of the studies but in that one individual here, you do see twenty two percent inhibition and you're correct, the other individual only had seven but in this these two individuals we have roughly about twenty to twenty two percent inhibition. There are limitations of the studies of course a few individuals and...

DR. LOWIT: The point of our bringing up the human study in Dr. Rease's presentation was in part

in response to FMCs comment that the twenty one day studies were consistent with other studies some of which being the human data and in part in exactly what you say in the spring, we disagree with that conclusion.

We didn't intend to begin the debate of if you were going to use it which section you would use it and all the uncertainties around that because certainly the small sample size the very building upon this race probably the method they used was a host of reasons why that study is deficient scientifically, some of which I think would if you thought about it hard enough would lend you to think that the lower end of the LOEL.

If you are going to use it in a risk assessment may actually be driven lower had you had more samples or they used a better method so we didn't intend to open the debate about which is the right of the pieces but even if you use for example had we pulled out Phase B, which is a normal temperature humidity without the exercising at the dose of two if you use a thirty field uncertainty factor.

Which I think can minimally be warranted here, we're still an order of magnitude approximately lower than you would be having used the rat study and remember the point here is to protect workers in the

field and if we were to adopt the rat thermal study compared to that with a human we would be about a ten fold awake...we would be a magnitude away from something where it would be helpful...we thought it was protective of worker health, only just keep in mind that that's really the point here and the context we want you to think about that, that if the panel suggests that we...that our conclusions about the twenty one day study that combined of the RBC with a lack of a time course to assure that the peak was obtained on the data.

If that becomes your recommendation which then we have concerns about protecting workers and based on this data just let's keep, make sure we remember what the context is.

DR. LICCIONE: I also wanted to make another point of distinction between the human studies that last study and the 1978 study was done with a forty four percent active ingredient whereas the three phases of the other study was seventy five percent after the ingredients so we need to keep that in mind too.

DR. HEERINGA: It is correct that the HRSB has seen all of these studies and judged them scientifically unacceptable and I think we'll be able

to address that if the panelists choose in the context of our response the charge questions. Any other questions of clarification at this point? Dr. Bailey?

DR. BAILEY: I just have a comment about this acronym the DNR and it's been stated that the Do Not...does not replicate the word replicate is not it is unfortunate because to design of experiments that means that you repeat the experiment and our new study or that new individual new experimental unit and that's quite different from what would be called a repeated measurement of the same material from one experimental unit.

DR. HEERINGA: Thank you, a point of clarification. At this point I think that we're ready to move onto the charge questions and I'm going to try to guess who will be reading these into the record but someone will step forward, Dr Reaves or...I'm not nominating you.

DR. REAVES: Yes, I think I was the loser on the coin flip there. Okay. Number one, point of departure and FQPA safety factor determination for dietary risk assessment for infants and children and the 2000 human health risk assessment for carbofuran, the Agency used a benchmark dose (BMD) approach for one comparative acetylcholinesterase study adult and

juvenile PND 11 rats submitted by the pesticide registrant, FMC, to derive the point of departure POD for risk extrapolation. This study showed that PND 11 pups were more sensitive to carbofuran compared to adult rats based on brain acetylcholinesterase inhibition.

Although low blood cells acetylcholinesterase data were also provided in this study these data were determined to be unreliable. At that time the Agency applied FQPA safety factor based on the lack of red blood cell, acetylcholinesterase data in pups. The value of the safety factor was based on a five fold sensitivity of red blood cell acetylcholinesterase for carbofuran in adult rats compared to brain acetylcholinesterase inhibition, i.e., red blood cell, acetylcholinesterase was inhibited at a lower dose than brain cholinesterase. The Agency assumed that red blood cell acetylcholinesterase inhibition would also be more sensitive than brain that acetylcholinesterase in pups.

In the last year three more studies in juvenile rats have become available. One study was sponsored by FMC, two were performed by EPA's office of research and development ORD. The two FMC comparative cholinesterase studies and ORD's PND 11 study provide

remarkedly similar brain cholinesterase data and when evaluated in combination provide data from low to high doses. However, the Agency identified problems with the red blood cell acetylcholinesterase data from the 2007 FMC study.

Furthermore the ORD studies failed to provide red blood cell acetylcholinesterase data in juvenile rats at the low end of the dose response curve. The sensitivity of the red blood cells acetylcholinesterase inhibition in juvenile rats at lower doses remains uncertain.

Charge Question 1A, FMC the pesticide registrant, has sponsored two comparative acetylcholinesterase studies with carbofuran. EPA previously concluded that the red blood cell cholinesterase data included in the first study MRID466688914 were unreliable.

The Agency has similarly concluded that the red blood cell acetylcholinesterase inhibition data and the second comparative cholinesterase study conducted in 2007 MRID 47143705 are not sufficiently reliable for extrapolating human risk.

The justification for this determination is summarized in the issue paper and discussed in detail the data evaluation record DER. In brief the red blood

cells acetylcholinesterase data from this study were highly variable in all animals especially PND11 pups, with control values differing between component studies and even within a study. Moreover, re-analysis of samples due to failure of acceptance criterion likely led to less detected inhibition.

Please comment on whether, in light of the available scientific evidence, it is reasonable for EPA to conclude that the second comparative acetylcholinesterase study MRID 47143705 contains reliable brain acetylcholinesterase data for use in the human health risk assessment but not red blood cell acetylcholinesterase data.

DR. HEERINGA: We'll take these part by part as we did yesterday. Dr. Brimijoin.

DR. BRIMIJOIN: Okay, my short answer to that question is yes. I once stepped slightly outside the framework and EPA has a carefully scripted coach to the panel and sort of like a syllogism, we are supposed to work our way through it and I want to step outside that box.

Let me just preface it by saying that what we have here is the first of four pressing questions and they all deal with EPA's set of decisions that EPA has made in regard to these exposure data in rat studies

and the first decision is that in the AChE inhibition in PND 11 pups in the rat brain is a proper point of departure for the carbofuran risk assessment and there seems to be actually agreement between EPA and the registrant on that point.

Second and that's really the question here, question 1A a decision that the registrant's RBC cholinesterase data are not acceptable because of the reasons stated for replication limited inhibition lack of dose response, and other deficiencies.

Third that the ORD has better RBC data suggesting that in dose range tested is this still not live enough...okay, just hope I don't start reverberating so third ORD has better data suggesting that in the tested range RBC cholinesterase is much more sensitive in brains and fourth that applying a five hold safety factor to account for the difference between the RBC and the brain dose response curves will lead to a vast or a reliable estimate of BMD, and personally I agree with the first two decisions that the brain inhibition in the pup is the proper point of departure and the registrant's RBC data are not acceptable for the reasons stated.

I don't, I have trouble with both of the...both the third and fourth point and I'm not

listed as a discussant on all of those issues but I saw...I will probably try to bring in some aspects of my reasoning in the two questions that I am officially addressing so with regard to question one, not to...

I won't take very much time but I'll give a little ecumenical support of EPA's decision to reject the results of data from the registrant study, so since the early 1990's much effort has gone into the finding of standard operating procedures that would allow the laboratory to assess cholinesterase inhibition in the red blood cells after exposure to carbonate or OP pesticides.

And I have to say that to date this goal has not been fully realized and the difficulty in part reflects the fact that there's hemoglobin, that interferes with the classic spectrum metric assay and the absorption spectrum generated by the product overlaps with the hemoglobin that can't be gotten rid of and its difficulty is greatly compounded in samples from rats and mice which are seriously deficient in cholinesterase, their cholinesterase levels are only on the order...they're an order of magnitude lower than in human red blood cells so it's not all that easy to measure human RBC accurately.

And with rats and mice it's really quite

difficult and I think this present data merely confirms this point without very specialized attention, and a routine laboratory assay is going to have problems with variability and very low signal to noise ratios. Studies involving carbamates have to cope with the further complications of rapid recovery in vitro.

Since the rate constants for regeneration of N-methyl carbamate enzyme allow fifty percent recovery in less than an hour, about forty minutes in my lab. All these problems appear to have been operating in the sponsor studies on inhibition of RBC cholinesterase by carbofuran.

If the data were highly variable, in both cases the variation approaching fifty percent in some cases and of mean and partly as the result no significant reductions were observed in treating rat pups at any time or dose despite mean value shifts up to about forty percent.

Additional factors contributing to this unsatisfactory outcome as documented in the data evaluation record appear to be slow sample preparation, use of diluted samples to allow recovery, the failure to keep samples for two and four assay. Both on grounds of high variability and on the grounds of inadequate procedures, the RBC data are of dubious values, the EPA

is well justified in taking the position that the data on ACH inhibition in rat red blood cells particularly with the PND eleven pups are not acceptable to the purpose of predicting health risks from carbofuran.

The brain data from the same study are considerably more robust with much less variability in clear dose response relations so in summary I think it is reasonable for EPA to conclude that the second area AChE study and I won't quote its MRIG number contains reliable brain data for use in a human health risk assessment but not RBC AChE data.

Let's see, I'm...one more paragraph and then we turn to the other discussants but I think that what I will now say captures at least part of what Dr. Chambers and Dr. Kehrer have also thought on this subject at least part of it to amplify this or correct me if I'm wrong so the ... this is where I cross the line from questions one and two of the other questions, so these data are roughly in line with the brain data are roughly in line with those from the registrant's study. The registrant's study are roughly in line with those from EPA's ORD.

However, in the draft intent to cancel notice EPA finds be stated informative, the brain data informative but chooses to rely on internally generated

RBC data because of the study suggesting that this is the more sensitive end point.

This decision can be questioned because inhibition of RBC as to cholinesterase is at best a surrogate for toxicity elsewhere. It's a surrogate for toxicity at sites, outside the brain where enzyme inhibition generates acute toxicity, sub-sites include motor in places filled with muscle synapses and autonomic ganglia, heart, vasculature, and GI tract.

It is recognized that after uptake through dermal oral or inhalation exposure any pesticide must reach its tissue targets by bloodstream, it will therefore not be surprising if RBC cholinesterase were inhibited earlier or somewhat more extensively than the brain and also perhaps somewhat more extensively than muscle, nerve or other tissues. In fact this may be the case with regard to the carbofuran although the data on a variety of these carbamates shows that RBC ACP rarely more effective than brain AChE.

I think we're going to have to come back to this issue of whether the RBC data are reliable measures of RBC, AChE inhibition or not, how much weight we should place on the measure of inhibition and that in part in deciding how to modify estimates of B&B counterparts of departure and I'll stop there and turn

it over to the other.

DR. HEERINGA: Okay Dr. Brimijoin. Dr. Chambers.

DR. CHAMBERS: Thank you, there was a little bit of discussion that for disclosure purposes amongst some of us discussants. The short answer to the precise question is the same as Dr. Brimijoin's, the second comparative AChE study does contain reliable brain acetylcholinesterase data but does not contain reliable red blood cell data.

For the sake of transparency I want to indicate that the opinions that I'm about to or the comments I'm about to make, I came to before any of the discussions during this meeting right now, based on my many years of experience with organic phosphate antecholinesterases and this goes beyond the exact question also.

There's a concern that the red blood cell data are being depended upon for the human health risk assessment. The brain acetylcholinesterase is the target for the toxic effects of the n-methyl carbamate anticholinesterase insecticides and red blood cell acetylcholinesterase is not the target that we pointed out just a minute ago.

Red blood cell acetylcholinesterase is viewed

as a surrogate for the peripheral nervous system, acetylcholinesterase but definitive studies to discern the relative sensitivity of red blood cell acetylcholinesterase and peripheral nervous system acetylcholinesterase have not been performed. Brain acetylcholinesterase was used as the appropriate end point for the previously conducted cumulative risk assessment of the n-methyl carbamates because it is the target of toxicity and red blood cell acetylcholinesterase was not used as the end point.

The following are quotes that I found from the September 24, 2007 revised n-methyl carbonate cumulative risk assessments that we all produced. Quote, toxic potencies for the n-methyl carbamates were determined using brain acetylcholinesterase inhibition measures as peak inhibition following gavage exposures in rats.

Brain acetylcholinesterase inhibition is a direct measure of the mechanism of toxicity and thus does not have the uncertainty associated with using blood measurements of cholinesterase inhibition which serve as surrogates for cholinesterase inhibition for the peripheral nervous system. Furthermore relative toxic potencies derived from the brain data were shown in the preliminary assessment to be similar to those

derived from red blood cell data but showed less variability and thus less uncertainty when comparing potency across the n-methyl carbamates.

A second quote, the Agency has elected to use ten percent inhibition of brain acetylcholinesterase as a response level for the relative potency factors and points of departure. The ten percent response level is health protected in that no functional behavioral effects have been noted at or below the level in adult or juvenile animals. Thus the ten percent response level provides a point where functional behavior neurotoxicity is not expected, I'm going to quote from that document and offer my comments.

Therefore it is unclear to me why the rationale of using brain acetylcholinesterase being the most suitable and reliable information is used for the cumulative risk assessment and then brain acetylcholinesterase was not selected in this carbofuran risk assessment when reliable brain acetylcholinesterase data are available in both adult and juvenile animals.

The choice of red blood cell acetylcholinesterase seems to be based upon the appearance of greater sensitivity and inhibition of the red blood cell cholinesterase compared to brain

cholinesterase in in vivo experiments. So the question I was going to ask was asked before me I think by Dr. Kehrer and that was the answer, that it was more sensitive.

While this may be true, I'm not sure it's true, but while it may be true it is certainly to be expected and is readily explained in points that Dr. Brimijoin brought up a minute ago, blood encounters carbofuran prior to the brain and in oral exposure any cholinesterase present in the blood would be likely inhibited before the carbofuran could reach the brain. If inherent sensitivity that is in vitro sensitivity in addition is similar to plain acetylcholinesterase in the brain and red blood cells the kinetics in the experiment.

The kinetics in the in vivo delivery of the carbofuran to the various tissues would lead to greater inhibition of the blood or source of acetylcholinesterase first encountered in the brain. That's not too hard to fathom.

The red blood cell cholinesterase is not a target of toxicity; inhibiting red blood cell acetylcholinesterase does not result in nervous system dysfunction.

Therefore it does not seem reasonable to me

to choose a non-power end point for the carbofuran risk assessment with the inherent uncertainties of less reliable data and consequent extrapolation required when more consistent and reliable data on acetylcholinesterase in the target organ are available from several experiments conducted by different groups.

Again that's a little bit out of bounds of that question but I do think that those are logical responses, I do not understand the choice of red blood cells here when you have reliable brain data which is the target.

Because of that I have asked Dr. Heeringa to include an additional question that asks that particular question in the discussion if we feel that's not adequately covered during the rest of the questions.

DR. HEERINGA: Thank you and we will go through our discussion of question 1 before I speak to Dr. Chambers about whether to introduce that additional question. At this point I'd like to turn to the next associate discussant who is Dr. Kehrer.

DR. KEHRER: The good news is this will be a lot shorter because both of the previous discussants have covered everything that I considered on this question and then some and I think if we do

come back to the red blood cell cholinesterase issue I may have more to say but because I agree with Dr. Chambers on what she just said.

DR. HEERINGA: Dr. Reed.

DR. REED: So the short answer to this straightforward question is the same as my colleague in terms of the second FMC study contends useful information about brain cholinesterase but not the RBC and cholinesterase data for the reasons that have been stated. I suppose it is important to jump in with a RBC cholinesterase information in terms of, you know, whether it can be used for risk assessment.

I do want to bring to the attention of our group, our discussion today that, that I felt it's important that risk assessment should consider the entire data base of a chemical although what we have brought to the table today is only about free falling esterase and RBC cholinesterase and therefore we're trying to decipher you know which one is more appropriate or not.

In terms of the entire data base for carbofuran something that brought to my attention or our attention in our department is the clinical science that are no data are reported in some of the studies. For example, clinical signs that are attributed to

carbofuran treatment are highlighted in one of the studies which is summarized in our department's toxicology data review summary which you can download from the web site.

In a 1978 teratology study Breckland rate rats showed dose related increase in chewing motions at the oral gavage dose at 0.1 milligram per kilogram or above mouth smacking, chewing motions indicate neurotoxicity although it cannot be determined whether it's related to brain or central nervous system or the peripheral nervous system.

And so I did a then tried those analysis a couple of nights ago, the BMD 10 and BMD L10 for these end points are 0.04 and 0.03 milligram per kilogram day respectively and so I thought this brings into the discussion if we were go into it later on about the pertinence of using a blood cholinesterase data.

The other point I think that was brought up earlier was the apparent discrepancies between cumulative risk assessments and methocarbonate and for carbofuran risk assessments a single ten fold risk assessments. I felt I participated in the cumulative risk assessments and methocarbonate discussion also and my understanding is that for doing cumulative risk assessment you are trying to find an endpoint that is

across the board for all the cumulative chemicals that has relatively solid data base for relative potency comparison but that does not limit using different end point if a chemical should be found to be more sensitive to use a different end point for a single chemical risk assessment.

And therefore, I agree with the Agency's decision to use red blood cell cholinesterase inhibition as an end point for carbofuran and yet using brain cholinesterase data for cumulative because across the board for in methocarbonate and for the reason that RBC data often were in a sense unreliable depending on the method of measurement that I agree that the two between the single chemical and the cumulative risk assessments the two end points can be different and expounded.

DR. HEERINGA: Thank you, Dr. Reed. Other comments from the panel. Dr. Edler?

DR. EDLER: Yes, thank you. I just think I have three small comments to the obviously AChE data and I think it's perhaps best to have them at this point because it's a little bit overlapping but other than that I've got three other points.

DR. HEERINGA: That's fine.

DR. EDLER: The first thing is I think

we also saw in theology of the RBC data when compared to the brain data inhibition by the observation that the correlation between motor activity seemed to have been better with the brain data than with the RBC data. It's a small I think it's a small observation but it might be, it should be at least mentioned I think.

The second thing is the use of the RBC data is critical since the health effect that may be directed, directly related to the RBC data have not been very substantiated at least at this time by reasonably good data.

If you look at the NIOC document it mentions some adverse effects like gastrointestinal or cardiovascular effects but this is very weak and the difficulty with those end points is of course that the power to detect those effects when using these qualitative end points it's much lower than you use data which had a continuous end point therefore and those more powerful studies to look to make a relation or correlation being the obviously inhibition data and gastrointestinal or cardiovascular effects are just not available.

A third point that has already been mentioned is this non monotone behavior of the dose response relationship at least in some experiments and this is

just I think still not explained from the statistical design or conduct of a study point of view. It could have several reasons, amongst them are just deficiencies of the design, perhaps there are other deficiencies of the conduct of the experiment or just the large measurement errors we had discussed already and Dr. Reed also mentioned that means the measurement error if you used the modified colorimetric method or the regular metric method.

And this has I think this has already been discussed in the SAP meeting on February 2005 and I also agree that with what has been said earlier that we are not dealing with a specific compound, we are not dealing with a cumulative risk assessment, so I am not likely to have any problem with that. Thank you.

DR. HEERINGA: Dr. Hattis.

DR. HATTIS: Yes, I don't know if we are going to get into things that are appropriate for the subsequent portions of this. Dr. Kehrer sort of mentioned the issue or the assumption that's shared by the EPA that the BNB 10 is a protective end point for uses of point of departure and I guess I want to introduce some motive of data on that point.

I think it's right that it's a protective end point for acute toxic anticholinesterase responses but

I think that there's reasonable doubt that it's a protective end point for developmental changes that are specifically within the purview of the...that part of the concern about the two fold extra margin of safety of ten, so I think I'm basically going to defer to this paper by, recent paper in press by Yang. I don't know if now is the time to explain what that paper says.

DR. HEERINGA: I think we have an opportunity, do we not, under 1-C maybe to address that, Dale?

DR. HATTIS: Yes, either B or C is fine.

DR. HEERINGA: No, let's do it there so we don't...

DR. HATTIS: I just wanted to thank Dr. Chambers.

DR. HEERINGA: No, just to be clear and make sure we get everything in and if it somehow doesn't fall naturally we'll cover that. I think what I'd like to do at this point is to move to Item !B if the primary discussants are satisfied at this point. Dr. Brimijjoin?

DR. BRIMIJOIN: Just a question for a panel member Dr. Reed. So I agree with you wholeheartedly that we should be making, we EPA should

be making decisions based on all the available evidence and you brought up this interesting point in your review of the literature on basically neurotoxicalogical measures from which you derived an apparent BMD10 lure 0.04 or so. This however fits not with the RBC DNBL 10 but with the brain DNBL ten as I recall so in fact if we do take a bigger picture approach that would tend actually to move us maybe in the direction of Dr. Chambers and I are and Dr. Kehrer were advising you is to learn more or to place greater weight on the brain data than on the RBC data.

DR. HEERINGA: Dr. Reed

DR. REED: Sorry the data actually was not about young rats, these are pregnant rats so the data or the BMD10 that we were referring to here that is the basis for EPA's risk assessment or point of departure is actually derived from young rats yeah so there is some difference between the two , I don't know the sensitivity between the pregnant rats and the young rats but we're not...I mean the BMD10 and BMD L10 are similar but they are not for the age group that were considered as more sensitive perhaps.

DR. HEERINGA: I'd like to move on to Question 1B, Dr. Reaves.

DR. REAVES: Question 1B, the

exponential dose time response model used by the Agency to derive BMDL or BMD 10 and BMDL10 estimates for carbofuran is similar to the model used in the NMC cumulative risk assessment and previously reviewed and supported by the SAP on two occasions FIFRA SAP, 2005a,and b.

For the carbofuran risk assessment the Agency's dose response analysis for brain acetylcholinesterase in PND11 pups included data from three PND11 studies two FMC supported studies and one EPA ORD study and thus provides robust estimates for use in the point of departure determination. Conversely the Agency's red blood cell acetylcholinesterase dose response analysis for PND 11 rats only includes data from one EPA ORD study where only high doses were used.

The BMD and BMDL estimates for red blood cell acetylcholinesterase activity are not high confidence estimates as they are extrapolated over fifty fold lower than the lowest tested dose in the EPA ORD PND 11 study.

Please comment on whether the scientific evidence currently before the Agency supports the Agency's conclusion that brain acetylcholinesterase data provide a more robust point of departure than the

red blood cell acetylcholinesterase data..

Please also comment on whether the scientific evidence currently before the Agency supports the EPA's conclusion that the Agency's benchmark dose analysis of the brain acetylcholinesterase data from three studies provides a scientifically appropriate basis for assessing carbofuran risks to infants and children.

DR. HEERINGA: Dr. MacDonald.

DR. MACDONALD: The numbers to consider in answering this question were tabulated as EPA and FMC net analysis estimates in the Agency presentation. Information on the data used in the model and calculation applied to arrive at each BMD 10 and BMDL10 in the table were disbursed to wrote the material we were provided in advance in some cases not provided so I'm grateful to the Agency for providing clarification during the meeting.

Unfortunately the FMC documentation method of analysis of benchmark doses for acute oral exposure to carbofuran did not reach us until Thursday afternoon There are two problems with the RBC data, one the small sample size ten equals thirty and lack of low dose data in the EPA ORD PND 11 study and two short comings in the FMC studies as identified by the Agency. It is disappointing that the Agency put considerable effort

into modeling the data interpretation but not in the time available to get better data for PND11 RBC.

The result of weak data in an honest analysis is an extremely low DNDL10 for an RBC in juveniles. This is more a statement of our ignorance than it is an indication of juvenile through all this magnitude more sensitive than adults.

I don't think that this evidence alone demonstrates that the RBC data should not be used. Use of RBC was discussed extensively in response to Question 1A but it strongly suggested that the data from the RBC studies presented here are inadequate or inconsistent or both and do not give reliable consistent estimates of DMD10 and DMD L10 especially for juveniles.

In contrast the brain data showed remarkable consistency between EPA and FMC analyses. Furthermore because the sample sizes are adequate the BMDL 10-values are much closer to the BMD 10 values than they were with RBC. The Agency's data analysis and model fitting are well documented.

Although this is out of my area of expertise I do not see how we can say with any confidence that the difference between adults and juvenile rats can be extrapolated to the difference between adults and

juvenile humans.

All in all it appears that the Agency's benchmark dose analysis of brain acetylcholinesterase inhibition from three studies provides a scientifically appropriate base for assessing carbofuran risk to adults into infants and children provided that suitable safety factors are included.

DR. HEERINGA: Thank you, Dr. MacDonald. Dr. Edler?

DR. EDLER: Yes, I totally agree with the overall statement of Dr. MacDonald about that so I won't go into that once more or state that yes, that's the truth or the discretion. I want to make a remark on the data and the results presentation when it comes actually to the final presentation when you go to the ADAD. It's easy to report the safety factors actually but a bit more complicated when you go actually to the point of departure.

Because you have three levels of data and it was already mentioned that we don't have the first...it's difficult to get the data and these are the original data which at this time are deep in the files and although these are not so many data but see then the next level are the single DNDs and DNDLs of each studies which actually could be more than one pair

of several models which would be applied to calculate those DNDs and DNDLs and the third level is that what we actually saw in the slides here mostly, namely the DNDs and the DNDLs as a result of a meta analysis sometimes using a different number or different types of studies.

It's feared that in the process as the present one there may be still some missing parts so I think we have just to fill these parts or depths or depth finally comprehensive picture that has been done when these DND analysis has been prepared and how you get actually to these couple of final figures and I think we will get just one figure .03 where we actually would stop but we need to know the way and the path we've actually went to that.

I have a couple of other comments through the method itself but I'm not sure if I should read them all but it says in principal that the method was well done, the application of the PND requires a careful selection of the benchmark dose response, that means they take the five percent or the ten percent that the EPA has taken the ten percent which was pretty wise to do that so there is no big problem.

That usually when you have continuous data you can go a little bit step further and use all of the

five percent level but I think we talked already about the missing of the low dose data so at the moment we might not prove that to go to the five percent level as there would have been more data once you have e done. once you and go to the five percent level.

The PND approaches by the Agency for these continuous data but it's financial dose times response model this is a new model it's just been very recently into the PND software and it's actually a good thing to have it than..because when one has more models in the ball park for the continuous data, the linear ones, the polynomer, polymer and the hill model but it also shows you that there is a choice, a model choice in doing the PND analysis so we have to be careful.

We actually, one has to justify and to explain what's there on the why one uses, selects this model and not the other model and this is one of the information that's easier at the moment but overall the visual inspections we have from the data at least from the remote documents provided by Dr. Setzer says that it seems to be a reasonable fit, that's all that we can pretty much rely on these days. Thank you.

DR. HEERINGA: Dr. Bailey.

DR. BAILEY: Ted Bailey, I have nothing additional to add.

DR. HEERINGA: Dr. Hattis?

DR. HATTIS: I also agree that the brain acetylcholinesterase inhibitions data are stronger both in being less uncertain and more directly appropriate for detrimental effects. However, a close examination of the results leads to some additional findings of difference from Dr. Setzer's analysis. Dr. Setzer's analysis indicates that not only...

DR. HEERINGA: Dale, could you pull your mike just a little closer. Sorry to interrupt, make sure that everybody can hear and Gary can hear too.

DR. HATTIS: Dr. Setzer's analysis indicates that not only did the PND 11 animals have a lower peak that's cholinesterase inhibition but the...by about 1.8 fold or so a central estimate but they also have slower recovery probably more than four fold and so both of those factors would influence the area under the curve of brain cholinesterase inhibition and although I think there's been extensive discussion that if you consider carbofuran alone it's unlikely that you have more than one eating event per day that gives significant inhibition.

This is not the carbofuran is not the only cholinesterase inhibitor that is present in the diet

and also you have the possibility that repeated exposures to milk and other items that are frequently consumed by young kids you know could add up to a much more frequent dosing than would be necessarily protected by the acute.

The other issue with the choice of the dosimeter is that we don't know whether the acute effects, the acute anti-cholinesterase effects are really the effects of greatest concern, so I'll talk a little bit more about nerve developmental issues that relate to this other paper but anyhow just leaving aside the fact that there's a choice of dosimeters and we're not completely sure which is the right choice for this case because we're not completely sure of the detailed mechanisms of action for all of the effects.

And as well as the dosing patterns, so if in fact, you combine the relative sensitivities indicated by Dr. Setzer's analysis then both factors are important. And they act more or less multiplicatively so you get sort of a central estimate of eight fold or so enhanced susceptibility with confidence in a five percent, ninety five percent confidence limits of about five and a half to fourteen or so for the area of the curve pipe dosimeters which I understand is not the preferred dosimeter for the anti cholinesterase agents

as indicated by the Agency.

Beyond this there is reason to doubt that the protectiveness of the standard grain acetylcholinesterase DND 10 lower confidence intervals estimates a point of departure for safety assessment and I think that it's fine as a statistical mallet for comparison to lone potencies of anti cholinesterase agents and for ordering, you know, for calculating the relative potency, you know.

And for doing your basic calculations but whether it really represents a safe level for is I think open to some question in the sense that a recent paper in press Yang et al that is distributed to the other members of the committee indicates that an important reduction in axon growth in in vitro systems by another class of cholinesterase agents, the chloropyrophos which is a, a phosphate and dioxyl, which is an oxidated, oxidite form of that.

Basically you get these a serious reduction in this ability of the axons to extend themselves at levels of exposure in the medium at least an order of magnitude below levels where you get the detectable acetylcholinesterase inhibition.

That doesn't mean that there isn't some cholinesterase inhibitions, likely there is, but this

does seem to be an endpoint that has some faith validity for developmental changes that's occurring when only a small fraction of the cholinesterase endpoints molecules are inhibited.

The paper is particularly good in the sense that there they show that this effect is very specific to the acetylcholinesterase enzyme itself both by the use that it's showing that the effect goes away if you derive the same cultures from the base of ganglia of knock out mice where, which don't have the acetylcholinesterase enzyme and by restoring the function and the inhibition of the function from chloropyrophos by transfecting in functional copies of the acetylcholinesterase enzyme and also showing that if you transfect in instead of a functional copy.

A copy that doesn't have the active site of the enzyme mutation, of the active searing which is the site of action at the prostates and the columnates if you change that to an ALMI, it loses its, so it's a very good demonstration of this, that this is related to acetylcholinesterase enzyme, active enzyme but occurs at apparently at levels where pretty much less than ten percent of the enz -- well, that pretty much less than where you have the detectible enzyme inhibition.

For whatever reason and because of this I think there is reason to doubt that there is sufficient information at present to meet the statutory standard that a FUPA factor of less than ten will be adequately protective for human health.

DR. HEERINGA: Okay. Dr. Reed.

DR. REED: Since the benchmark response issue was brought up by Dr. Edler I just want to add that I agree with the recommendation or the opinions that it's not necessary to lump the benchmark response for brain cholinesterase at ten percent for a couple of reasons.

One is that for many data sets in general not specific to carbofuran that statistical significance can be seen that for low detect response, also that as we have more regional data become available, we see that not every region of the brain has been predicted at the same level so this is again agreeing with what Dr. Edler say, said but not particularly for recommending the agency to use a different response but I think the issue is important enough that they agree on.

DR. HEERINGA: Dr. Edler.

DR. ADLER: Just that I agree with this thing. That I agree with this thing.

DR. HEERINGA: Dr. Chambers.

DR. CHAMBERS: I have not read this paper that Dr. Hattis is just referring to but I do want to caution the Agency of equating the n-methyl carbamates and the organophosphates. The organophosphates and n-methyl carbamates have very different chemistry, very different metabolism, certainly persistence of their effects are very, very different now so.

Again that may be merit critique, I really don't know but I just, I really caution just equating organophosphates and the n-methyl carbamates.

DR. HEERINGA: For the sake of the audience's information to, let me just give you the citation it is in press accepted manuscript in toxicology and applied pharmacology to appear I guess is it available electronically,

DR. HATTIS: Yes, it is available electronically and if you need to buy it.

DR. HEERINGA: But we have a copy here it will be I don't know if it can be placed in the document...I don't know about copyright, so if anybody wants to see it. At this point Dr. Brimijoin had an additional comment.

DR. BRIMIJOIN: Same topic I had a

chance to look at the paper yesterday, I read it, it's very interesting but I agree with Dr. Chambers it's not really relevant to the present issue.

It deals with chloropyrophos, an agent with different chemistry and one for which we have at least a lot of cumulating smoke if not actual fire and flame to indicate potential for developmental or specific, chemical specific that then you can, we should also.

We may be prepared in the back of our minds that if we end all these deliberations on carbofuran is cancelled, chloropyrophos is one of the agents in the HNP with discretion to move in there.

DR. HEERINGA: At this point in time I'd like to move on to Question 1C. Dr. Schlenk?

DR. SCHLENK: I wanted to present this now or at the end of four I guess but one of the things I was very interested in and I think as the question indicates is the brain cholinesterase data indicative of protection of infants and children and one of the points I think that didn't get addressed I think and I want to make sure this is on the record all the studies that were done in the PND 11 studies did not tie cholinesterase inhibition to toxicity event. I just want to be sure that's clear.

It was done in the PMD 17 study her motor

activity was correlated to brain cholinesterase inhibition and RBC cholinesterase inhibition and that's the only place where there was toxicity that was tied to cholinesterase inhibition.

PMD10, PMD11 studies unless I'm missing something there was not a correlation of toxicity with cholinesterase inhibition so just I think that has to be sort of put on the record that you're extrapolating toxicity from one stage to another stage with those data and that was not done in this particular case and I don't know given the differences in the adults and the PND 17 whether or not we could do that extrapolation from the 17 to the 11.

DR. HEERINGA: Dr. Lu.

DR. LU: I think the agency answered that question on the data it presented. It's a PND 11, the age of the rat is too young to be able to perform those tasks. That's my understanding so to avoid to making some error in data, that's why they don't, they don't do that kind of thing.

DR. SCHLENCK: I understand that but there are other mechanisms of toxicity and other endpoints of toxicity that could be addressed for cholinesterase effects that could have been evaluated. Motor activity is just one measurement, there's a host

of other things that could have been evaluated as far as toxicity is concerned.

DR. HEERINGA: What I'd like to do I had indicated I wanted to move to 1C but I think that maybe it's time for a fifteen minute break and come back at 10:20 and then we will turn to question 1C. This is to help people plan, it's ...I'm not going to restrict discussion but if we approach the noon hour with what I feel is about an hour left, I probably will go through the noon hour for that.. If that doesn't appear to be feasible I will call for a lunch break

(WHEREUPON, a brief recess was taken.)

DR. HEERINGA: Okay, we are set to start again in just a moment. Okay, I think we're legitimate and legal here now. We are. We're still waiting for Dr. Brimijoin. Gary, are you back on with us?

DR. ISOM: I'm on now.

DR. HEERINGA: Thanks a lot, I appreciate it. We're ready to get started here in just one moment. Okay, now we're ready to resume the continuation of the final morning session of our four day meeting of the Science Advisory Panel. We have entered into a series of charge questions related to human health risks, we have had responses to questions 1A and 1B and we're turning now to question 1C, Dr.

Reaves if you would read that into the record for us.

DR. REAVES: Question 1C as noted above in 2006 the Agency was concerned that red blood cell acetylcholinesterase inhibition was a more sensitive endpoint than brain acetylcholinesterase inhibition in both adult and juvenile rats.

This concern was based on a more limited data set of developed rat data available at that time, one FMC study. With the availability of the new acetylcholinesterase studies from FMC and EPA ORD more data in both adult and juvenile animals have been evaluated.

Based on the more extensive data the Agency has concluded that for adult rats red blood cell and brain acetylcholinesterase are similarly sensitive. In juvenile rats the lowest dose tested in both EPA ORD studies PND 11 and PND 17 resulted in approximately fifty percent red blood cell acetylcholinesterase inhibition.

At the BMD 50 red blood cell acetylcholinesterase activity was three to five fold more sensitive than brain and acetylcholinesterase activity. OPP had concluded that there are remaining uncertainties surrounding the dose response relationship of red blood cell cholinesterase following

carbofuran exposure in juvenile animals.

Please comment on whether you agree with the Agency's conclusion that, based on the available scientific evidence, there is remaining uncertainty regarding lack of dose response data at the low end the dose response curve for red blood cell acetylcholinesterase inhibition with respect to extrapolating risks to infants and children. Please provide a basis for your conclusion.

DR. HEERINGA: Dr. Macdonald?

DR. MACDONALD: Well, several of us have already addressed this question in response to question 1D. The dose response analysis done by the Agency for the EPA ORD PND 11 study is appropriate and leads to a very uncertain PND 10. The PND L10 being orders of magnitude smaller than PND 10 indicates the uncertainties. But the situation is even worse than that.

The extrapolation to PND 10 and the confidence interval calculation for BMD L10 are based on an assumed dose response curve. The curve fits well in the region where there are data but there's no way to validate that at low doses so we can't be sure that the extrapolation is valid other than to note that the curve fits well over a wide range of doses for adult

data.

DR. HEERINGA: Dr. Bailey

DR. BAILEY: I agree completely with the comment of Dr. Macdonald that the data from these three EPA studies has deficiency and they don't have the data the lower range of the dose response curve.

DR. HEERINGA: Thank you Dr. Bailey. Dr. Hattis?

DR. HATTIS: I basically concur that at particular uncertainty in the projection I do have a bit more confidence than the other suggested in the model because it's been so relatively well explored by the relative expert folks and so it draws upon a wider body of information than just these particular data and I think it's pretty well behaved and also has a theoretical basis that's not often well advertised.

So I do think the lack of data is probably reasonably well estimated by the confidence limits of, you know, at least it's common compared to other dose response relationships but there is still quite a lot of uncertainty indicated by those different endpoints.

DR. HEERINGA: And by theoretical it's still in the scientific basis related to that.

DR. HATTIS: Yeah, the essentially when Dr. Setzer developed the model he used a

McHale's/Benton type theory and you know enhanced to that below end four by allowing the power to vary and that's lots of flexibility in that model but McHale's method theory is reasonable for the enzyme inhibition as a mechanistic basis although it's not claimed to be a mechanistic model.

DR. HEERINGA: Additional comments or contributions on number 1C, yes Dr. Lu

DR. LU: I looked at those graphs for the long period and tried to make sense of it, and my conclusion is that if you look at the lowest dose on the RBC and the brain tissue the sequences that you can call it uncertainties but I looked at it as this is probably the true data in terms of if you look at the biochemistry reaction of inhibition in red blood cell versus brain, that twenty percent or three to four frequencies may tell you that there are very limited reactivations in the brain tissue.

We cannot quantify many and what kind. And this actually if you go back to Agency's ACHD data it shows that if you look at the dose at one milligram per kilogram a challenge on the PND 17, from zero to forty five minutes there's actually no reactivation, the inhibitions were going on so what does that tell you, it tells you that.

I mean some call it uncertainty, maybe there is a true fact in terms of inhibition in the brain tissue that does not show up in the red blood cell and so in other words, in other words to interpret a result is that there is a dynamic reactivation going on in the red blood cell but there's very little reactivation in the brain tissue.

So what is, what's important, is this, is the reactivation important or do we think it's important? So in this case I think it's...I wouldn't call it uncertainty, I think that's a fact, it's a matter of which aspect you want to look at, are you going to look at the inhibition in the end point or you want to look at the reactivation in the red blood cell that you can measure in the different kind of care.

DR. HEERINGA: Dr. Brimijoin and then Dr. Edler.

DR. BRIMIJOIN: I'm not sure if I caught the point of Dr. Lu's remarks correctly but Dr. Lu, are you referring to the registrant's data or the ORD data?

DR. LU: I'm looking at the ORD data.

DR. BRIMIJOIN: The ORD data and you're saying that you reactivation in the red cells because they show less inhibition than the brain. I thought it

was the other way around.

DR. LU: No, what I'm saying that you see a seventy percent inhibition in the brain tissue but only fifty percent inhibition so obviously there's a twenty percent differences and as a matter of how you interpreted these twenty percent.

DR. BRIMIJOIN: Wait a minute the ORD data supposedly shows the red cells.

DR. LU: It's a seventy...it's a thirty percent inhibition versus fifty percent. Thirty percent in the brain, 50 percent in the red blood cells.

DR. BRIMIJOIN: Okay, so that's backward then

DR. HEERINGA: Dr. Edler

DR. EDLER: I think at this stage we are still basically in a period of collecting data and doing the bench mark analysis so I think talking about some mechanistic aspects might be too early or might not be supported by enough data or could perhaps go to those kind data and then look at what can be done in a more mechanistical modeling, but I'm not sure how far this is actually let us now go than doing actually the risk assessments. I totally agree with what has been earlier said about the RBC data.

I think I only want to make another comment if you go perhaps go to the brain data and you then to also ask what's going on at the low end dose response area and of course it would help to increase the data base at the low dose area to improve the dose response modeling, it would add precision to the BMD, would add precision to the BMDLs so the distance between BMD and BMDL would actually get smaller.

But if you relook at the moment what we saw already in the data provided by the Agency, the distance between the BMD and BMDL is very slow and narrow so if you compare the other risk assessment I think you could be pretty happy to have such a small distance so for me the question is much more where to spend more efforts or more money or more experiments in either getting this distance even smaller or looking at actually for another end point, it might be more readily.

DR. HEERINGA: Dr. Bailey?

DR. BAILEY: In the EPA studies the RBC AChE is more sensitive, that is to say it's inhibited at lower levels of carbofuran than brain AChE. However the EPA studies did not include data at the low end of the dose response curve, the area on the dose response curve most relevant to risk assessment.

It is for this reason that significant uncertainty exists in estimating the BMD10 and BMDL10 or the EPA study so there's a simple, I mean an explanation that doesn't go into the behavior of the enzymes, it's just simply there and it's such a low concentration and that we didn't have this at the low end of the response curve.

DR. HEERINGA: Thank you, Dr. Bailey. At this point I'd like to move on to Question 1B which I'm sure will generate considerable discussion. Dr. Reaves, if you will read that into the record please.

DR. REAVES: Question 1D, the FQPA requires EPA to apply a 10 X safety factor for infants and children but the Agency may use a different margin of safety for the pesticide chemical residue only if, on the basis of reliable data, such margin will be safe for infants and children.

The Agency applied a 5X factor based on ratio of BMD50 estimates in brain acetylcholinesterase and red blood cell acetylcholinesterase in juvenile and animals. Based on the currently available data does the panel agree that basing its safety factor on the ratio of BMD 50 estimates in brain acetylcholinesterase and red blood cell acetylcholinesterase in juvenile animals is a reasonable approach.

Please provide a basis for your conclusions.

DR. HEERINGA: Okay, Dr. Brimijoin.

DR. BRIMIJOIN: I want to preface my remarks by saying I think it's really important that we're trying to make a comprehensive and maybe final judgment about what to do with a given chemical on the basis of extrapolations into thumbs of uncertainty and so at the 2005 SAP February meeting in human risk assessments I was struck by the tremendous weight that was going to be placed on BMD10 values and estimates of the lower ninety five percent confidence limit of those values at the point of departure.

I was struck by that because Dr. Bailey has just said frequently we don't have data even extending into that zone.

This is such a case, when it comes to the RBC data which EPA proposes to use, so of course there are all kinds of extrapolations which in themselves induce uncertainty and even when we have data in that end of the dose-response curve, those data tend to be noisy and variable so it's not at all unusual to find that the difference between BMD10L and BMD10 is an order of magnitude and carbofuran is in the higher end of the range of the variability so this presents a real challenge and it makes me wish that we had accurate

estimates of the BMD10, would narrow confidence intervals.

And I hesitate to bring this up because it may seem like self-advertising, and I don't mean it in that sense but I spent the next couple of years thinking about this issue, when we devise an experimental method, different method, which like all new methods requires validation and confirmation in testing but it has passed peer review at least of a way to get the BMD10 measurements with narrow confidence limits, and we tried it on a series of carbonate pesticides specifically so that's the problem where you have these rapidly reactivating agents.

It's hard to measure precise levels of inhibition and I dearly wish that carbofuran had been one of those pesticides that we chose to explore in depth and what not so I have no actual data to add at this date.

But, I mean, I just wanted to register well not a plea that the community of investigators at ORD and registrants and elsewhere gives really hard thought to this question of how can we really accurately estimate the inhibitions because I'm quite convinced that we don't have, the standard methods are leading us, if not into making mistakes, at least they are

leading us into an area where uncertainty will be large.

Now I would like if we could get the one slide that I brought with me and is now on the desk top up here I've got two questions. One is whether we should rely on the RBC data at all or go with the brain, and the other is if we rely on the RBC data do we accept this safety factor five fold that has been modeled by Dr. Setzer and I would hate to go one to one with Dr. Setzer in any kind of modeling exercise and I'm a rather simple minded pharmacologist.

And, I could not help taking the confusingly plotted data that is in EPA's own draft notice of intent to cancel and replotting them on this semi log plot, these are ORD data, replotting them on the semi log plot so I can see just how big the shift looked and lo and behold what I got was nothing like a five fold shift.

It looks like a two fold shift, now to state that we should correct the brain data with a two fold extra factor based on the RBC inhibition requires us to make other assumptions that what appears to be a parallelism between these curves in the range of doses actually tested still holds as you get to the low end.

That's an assumption.

I guess I would start with that assumption but obviously it's unproved and I'm sure that Dr. Setzer's model which includes all kinds of passage aspects it is indeed predicting a divergence at the lower end of the curve, but I would respectfully submit that that's just the end of the curve where we don't really know what's happening, so for my money a two fold shift is a more reasonable guess but the actual difference between the inhibition curves and the BMD11 pup, RBCs and brain and this is I admit I don't have the raw data sheets in front of me and I am working with numbers I pulled off the EPA's own reports .

So having said all that, I think that the most reasonable approach is to make a decision in light of the best available information regarding the possibility that younger individuals are more susceptible than adults to cholinesterase inhibition by carbofuran and there's more than one way to reach that goal and basically they are all imperfect.

If we had good data from adult humans, had the useable data from adult humans then that would be RBC data and also from both adult and juvenile rats, for example, we might want to use the age dependence of sensitivity in rats to adjust the PoD obtained in

humans.

Alternatively you could start with point of departure obtained from juvenile rats especially if it could be more sensitive than adults and adjust that factor value by an interspecies protection factor which would be, by default it would be a ten fold factor or less if that were well justified and I suppose the only way that we could justify reducing that safety factor would be quite strong evidence that one or more surrogate organisms such as a rat showed notably smaller differences and notably less age tendencies and that the interspecies we would need human data to reduce the interspecies factor.

So in the present case EPA has been advised by the scientific review board to ignore the human data and I have no comment on that decision in fact both Dr. Chambers and I, because of earlier remarks on this issue did not, were asked not to participate in that decision and I will make no comment.

I'm not allowed to, and I have no comment so in the absence then of human data EPA has taken an interesting but a complex and Hindberg approach which is less than satisfying because it is based on the inhibition data from a non target tissue rat RBC AChE which nothing's been said about its merits and it's a

problems as a surrogate for end cholinesterase toxicity.

Now I'm going to state that something that may be incorrect and if it is I refer to data from Moser and others and Dr. Moser's in the audience so if I'm misspeaking, I'll dare to take a stand here and if I'm wrong I beg to be corrected but it is my understanding that Dr. Moser and others have shown that RBC cholinesterase inhibition does correlate with inhibition and enzyme and other tissues and it does correlate with pure behavioral science toxicity in animals where that's feasible to possess.

But, I don't believe that anyone has shown that RBC inhibition is better than brain inhibition as a predictor of toxicity so in fact it hasn't been shown to correlate more tightly with inhibition and a peripheral hearty tissues that's partly because we don't have very much data out there on purple hearted tissues despite some interest in getting that data.

These are the reasons why I would prefer to stay with brain where there's a robust consensus between the RNB and the registrant data on illustration in the PND11 rat brain a real target tissue that does appear to be moderately more sensitive than the adult rat brain so if.

So, my bottom line is that I would either use this brain data as such or a smaller correction factor than the five fold factor to account for the apparent enhanced sensitivity of the red blood cell and, but I would use that as a correction for sensitivity, not, not as an, not as a, well, I would use that as the FQPA factor and I would apply the interspecies correction factor of ten fold and reach what I think would be a defensible point of departure and incorporate that to EPA's protection.

DR. HEERINGA: Thank you Dr. Brimijoin. I'd like to turn next to our first associate discussant and that's Dr. Reed.

DR. REED: Just to make sure that the scale on that is too hard to see and it's so far away. Dr. Brimijoin will you be providing some context where you came through and that sort of thing, or is this bracket

DR. BRIMIJOIN: This bracket I'll make this bracket is available I've got to phase it into my report, it's just my attempt to replot the same numbers that are on page 14 of your draft NOIC document and I just replotted them on a setting lot scale so the bottom scale is on the very left it's zero point, I mean zero one and the point one and one so the only

numerical unit there is semi lot scale and plotting residual AChE activity on the Y access and taking the data for the red blood cell and the brain.

DR. REED: I have just one point of clarification since the X is on the log scale...

DR. BRIMIJOIN: Right.

DR. REED: Which point along that line...on the scale they look parallel..

DR. BRIMIJOIN: See all those double arrows, they're all those double arrows are all identical width and I put them in there they are they correspond to the two fold increment and the two fold increment is on the constant width on a broad scale is a constant ratio I mean they're not exactly so the curves are not exactly parallel but they're pretty close.

DR. HEERINGA: The arrows are fixed length corresponding to two fold and the curves and the curves obviously deviate from the points zero but they may not be pretty clear. We will since this is obviously the display we'll make sure that a copy of this gets in the docket as soon as possible and more available so people will not have to wait for our report to see this

DR. BRIMIJOIN: I should also say that I

mean I did this with a compass you know and a ruler so there very well could be errors in this but it was intent to capture the data that were actually presented to us.

DR. HEERINGA: Unless your artistic abilities are absolutely atrocious I think the picture's pretty clear. So Dr. Reed.

DR. REED: Let me jump ahead and just make a comment about the graph that we have up there. I'm not a heavy duty modeler, so again I do not want to anytime worry about this either but the analysis that was done by the Agency and if there's confusion about this, I think it is important enough for the modelers amongst my colleague here for us to, Dr. Bedford, to clarify the differences because the FNC analysis.

Also, show, you know, a range of it being two fold, assuming a linear relationship with the exponent of one and since the exponent is not one, we're saying it's not very clear so this is as much as I want to say.

I think that it is important during this discussion, during this deliberation to clarify this point. Back to the comments about question 1D, I think by now we all agree that it is unfortunate that reliable RBC cholinesterase data are not available to

clarify the age specific sensitivities such that extrapolation can be avoided.

Given the lack of data in light of agency's assessment that acetylcholinesterase inhibition is a sensitive endpoint for public acute toxicity and based on all the data presented at the meeting I agree that the ratio of brain to RBC cholinesterase inhibition at DND50 can be used to determine safety factor for the end point of RBC acetylcholinesterase inhibition.

And I would like to just preface my comments based on the USEPA ORD's analysis about what the ratio may be and from the memo on February 4, 2008 from Dr. Setzer that appeared graphically to show that the ratios are approximately 2.5 to 7, in terms of range and with a central tendency of approximately four.

This result of data analysis support both retaining a painful EPA safety factor as a protective measure and the use of five fold factor which is closer to the same dependency. In general I think it is prudent to present both as a range and risk assessment.

DR. HEERINGA: Dr. Reed, you raised the issue of clarification from Dr. Setzer. I'm not sure that that's required here unless somebody is confused about what Dr. Setzer has done.

DR. REED: I agree.

DR. HEERINGA: I'll turn to the panel members who I ask to respond to this, does anybody feel they are uncertain about the nature of Dr. Setzer's analysis and presentation, the model fitting on the...okay, I think people understand. I don't want to shortcut this but I also don't want to --

I think that people understand the methods and they're both done then it's a matter of judgment. At this point I'd like to turn to our next discussant, which is Dr. Kehrer.

DR. KEHRER: Okay, thank you. I will start by saying that I do not agree that the basing of the safety factor on the ratio of the BMD 50 estimate of brain and red blood cell is a reasonable approach. I the...it's been discussed over and over that a red blood cell data is questionable use in many instances and they certainly have some real issues with toxicologic significance and I just cannot see the justification for improving on the ratio.

Well, it's been talked about in the model of a few minutes ago with Steve on the two fold that he came up with or Dr. Setzer's five fold, both of those were done with average data from the different animals. No one has yet brought up the suggestion by FMC that individual pup data should be used to do this

calculation.

By doing the calculations on the same measurements within the same pup to me are just toxicologically a much more valid approach and if you aren't even going to use the ratio then using that type of a calculation to me makes a lot more sense. FMC came up with I believe around a one point two to one point three ratio and that which is more closer to the two that Dr. Brimijoin came up with and the five that is currently being used.

If you want to go back to I'm concerned that the EPA when they traded those safety factor back in 2006 and they came up with five well I understood when I got a response to my question a couple of days ago was that they kind of said that that five was too much back then because now it's still five and the data are a whole lot better.

So, I just feel like the safety factor should be decreased based on the fact that the red blood cell data maybe shouldn't be used at all and rely simply on the brain data or if there's going with individual pups data which reported a much lower pup data which is reported a much lower EPA factor.

DR. HEERINGA: Dr. Chambers.

DR. CHAMBERS: I have difficulty dealing

with this question because it should be obvious from the comments I made earlier I don't think the red blood cell data should be used but if the red blood cell data must be used, then I concur with the earlier remarks, I think I'm not a modeler so I think the approach using the midpoint to the line probably would make some sense.

But I concur with Dr. Brimijoin's assessment thereto that they did not appear to me, I didn't graph it but the data don't appear to me to reflect a five fold difference, in much lower than that, so I disagree with the five fold factor because I don't think that was calculated based on the data. If you look at the data some of it, the red blood cell is not more sensitive than the brain in some of the experiments so I think I have a problem with that.

I also concur completely with Dr. Brimijoin's assessment earlier that all these extrapolations make me very, very uncomfortable.

DR. HEERINGA: Comments from other members. Dr. Lu and Dr. Edler.

DR. LU: It looks like I'm the only one that's supporting EPA's approach. I happen to have a set of graphs and I had a private discussion with Dr. Brimijoin after his presentation and I think I need to

put it as a pop quiz for the rest of the group.

If you draw the double arrow line vertically, for example, you actually have a very different interpretation and this is what I think. I of course, I would kind of feel like my interpretation is more accurate than other person.

I mean there's you cannot measure the dose sequences at a fixed response level in animal model, it's almost impossible so instead of drawing the line for example you look at the specific dose, you give it to the rats and try to determine the responses from the grand and red blood cell.

In the reality setting we cannot take a plant tissue sample from people it doesn't matter kids or adults so we have to rely on red blood cell measurement and I agree that the assay cell is very variable and a lot depends on a lot of variable factors which is protocol factors but based upon my logic say if I'm going to give you one dose for the rats this is what happened with the red blood cell for the end point is in the brain tissue so if we do not have the accessibility to the brain tissue then how can we estimate a brain, a response?

In this case, a safety factor of five will be somewhat reasonable to apply to in this scenario so

that's just my interpretation.

DR. HEERINGA: Thank you, Dr. Lu. Dr. Edler and then Dr. MacDonald.

DR. EDLER: Okay, I think we'll have to think about these graphs a little bit more. Actually I want to make a couple of points, but let me first start with the graphing. One may argue and I think it has been argued during the last days that whether the ratio of the two DNB's used in the risk assessment of carbofuran so far could be replaced by some other distance measure than these ratio of DNB 50 as done by the analysis of Dr. Setzer.

When attempting to do that you have to really to be careful about the statistical modeling and one thing you really see here is these are not the original data, these are the data normalized at the control and that's why you have the hundred percent on the top of that.

So for the DNB analysis actually uses the data as they have been apart from the experimental and from the lab so please be careful that analysis of the DNB is not the data you see here, these are the original data and they may look a little bit different and I think we actually see how they look if you look in the document we got yesterday from NFC and FMC

where they actually provides part of the original data in the field so look at that and you will see a little bit about what we are talking about.

So I really would encourage to use the entrance forms data of the dose response curve when discussing a distance between the two curves, that you actually do have a distance between the brain data and the RBC data. Of course this goes all under the caveat if we really want to do something with the RBC data that's, the discussion's a little bit pecking forth and back because you say, well, there are obviously there are other ways could we actually deal with that question, but given you one. use the unconfirmed data, present all of it as original data and then go to the graphs. I don't say that this graph, graph is not helpful, it helps us to actually understand things but it's not the only graph actually we look for when we do these analyses.

Another point I want to make the DNB and what's just alluded by Dr. Lu here, uses all the data and so we do a picture of the whole dose response curve and then we calculate the DNB and then we make this comparison and Dr. Setzer came actually out by the corrected analysis that's a factor, the best estimate he found was the factor of four.

He also talked about in that last document about the variability of this ratio and that was actually off this just a couple of minutes from now that looking at the paired data between the brain and the RBC, this has nothing done when you do the ratio but actually one can do something and that would actually then add to the variability of that ratio so if you go into this business actually and comparing curves then you really have to look on the variability of the distance measure you get using these paired data and I haven't seen anything about that so far.

The most what we saw actually there are more comparisons of means and but if you do comparisons of means then you have to go back to the original data, calculate all the variability you get, and then calculate the variability of the distance measure you actually have there. I know this throws in a tricky thing because this would actually holds the threshold. I use a safety factor like two or three or five or seven or whatever, what is the variability of this safety factor for the use in the risk assessment.

Now if you take the D410 we have no variability that's a ten but if you go back below ten you actually have to think about how variable is actually my fault. Thank you.

DR. HEERINGA: Dr. Macdonald and then Dr. Schlenk.

DR. MACDONALD: I can't help noting that the discussion of the safe dose is based entirely on observations of the acetylcholinesterase inhibition and recovery and attempts to interpret the data as precisely as possible. We have no idea what will be the long term health effects of chronic or frequent or low levels of exposure to carbofuran.

That alone in my opinion justifies additional safety factors with so much uncertainty it's not prudent to be working at the edge of what we think is safe.

DR. HEERINGA: Thank you. Dr. Schlenk.

DR. SCHLENK: I have a question actually just if I may to the EPA for this. Since it's defined as lowering at ten fold factor on reliable data if we find this data to be non-reliable does this automatically bump it up to ten automatically is that, am I interpreting that right?

DR. REAVES: Yes, that's correct, we are mandated to keep the ten unless we have reliable data to refine that Ten X. As you can see behind us that's saying, that's correct.

DR. HEERINGA: Dr. Hattis, I believe you

had a...

DR. HATTIS: If I was a much more authoritative statement of the legal to quote than I could possibly make. Essentially what as I understand it is a three fold protective factor is to protect against modes of toxicity that might happen for younger people or animals that are you know just not available in adults or observable in adults like the lead, you know, its developmental changes and things of that sort.

So, I think that you basically don't have the data base to be very fully persuaded that the difference in sensitivity for adults and rat pups, rat adults and rat pups is in fact reliably less than ten, under some interpretations of the data themselves you get eight if you have this A to Z type dose metric.

If you have just a peak you get something like two as a central tendency but still with some variability so I think that because of our additional pharmacologic uncertainty I think it's not easy to be, I'm not persuaded that we have enough reliable data to depart from the ten fold statutory factor.

DR. HEERINGA: Dr. Portier.

DR. PORTIER: Ken Portier here. I guess I'm just dense. I'm sitting here thinking this is a

factor that's supposed to relate uncertainty adult to, to child and yet all the data we're talking about is within the juvenile so the uncertainty we're talking about is uncertainty in end point response, it's not uncertainty from adult to child.

I would have preferred to have seen other middle carbonate comparisons maybe how does Aldacarb adult to child or something else and that would be more persuasive to me of reducing the safety factor than looking within two different end points within the same juvenile so maybe Dr. Brimijoin can explain to me why we're even having this discussion because I'm totally lost.

DR. HEERINGA: Dr. Brimijoin?

DR. BRIMIJOIN: What I was just talking about was measurements of the brain cholinesterase in addition. I mean I didn't go to the red blood cell at all. Beyond brain cholinest -- brain cholinesterase inhibition probably estimates some pharmacodynamic effect that is could be a little different if we hadn't got any measurements of that.

DR. REED: This is Doctor Reed, we'd certainly like to have more information so yes I think that the trouble, I think we're all easily confused, I've been confused over and over again by the kind of

conflation of interspecies and age related safety factors and so if we were going so one approach would be to take the adult rat data, apply a ten X safety factor for interspecies and throw in another ten X default safety factor for the FQPA effect.

That gets us through 100 X so if unfortunately I think we're all grappling with the issues of uncertainty. The point of using the juvenile pups was to see if there was evidence of a age related effect or putting it the other way around, to attempt to document that there was such an effect and assess its magnitude, and that's not what this curve addresses.

So, if we find that the evidence does not support, the evidence is not robust enough to take the brain data from the juveniles and either accept that as it stands and then go with the interspecies, assume that the juvenile brain data adequately reflects it or best estimate with all associated uncertainties our best estimate of what a young organ, young mammalian organism would experience and then we go from that back to human if we are going with a ten X interspecies factor. The second option is to take that brain data and correct it by an appropriate multiple.

If we make concession to the idea that the

RBC data are relevant we could correct it by I think a relatively small multiple and then do the same thing so that's starting from the juvenile end point and there's no more discussion about the FQPA factor.

Of course we can, new evidence may come to light at any time that any pesticide out there is in fact more dangerous than we know and acts by mechanisms that we haven't defined or even dreamed of but that's just the great cloud of risk that I don't think we grapple with.

If for any reason it seems to me but if the argument is not judged to be solid that that we've accurately assessed the level of effect in what we suspect to be the most vulnerable age stage and must say with full ten X EPA factor to account for that inability to pin it down then I think we should just go back to the adult data and apply the default factor but not apply the default factor through the juvenile data about which we are uncertain

DR. HEERINGA: Dr. Reaves?

DR. REAVES: I think this discussion is good I think it clarifies a lot of things but I think that the data that we are looking at right now is still about young rats, I mean post natal sensitivity the FQPA factor actually covers more than just post natal

but prenatal and we don't have a lot of data about fetal cholinesterase levels so in terms of how certain we are we are uncertain not only with being the data we have.

But, I have not seen a data that we don't have about prenatal sensitivity so regarding the earlier clarification about our FQPA factor or ten X should be retained only if reliable data indicating that such margins whatever margin that we choose can be safe for infants and so we're actually mixing some information or haven't talked about we're actually mixing some information or haven't talked about information we remind the panel about this.

DR. HEERINGA: Thank you Dr. Reaves, I guess I'll turn to the EPA now. There clearly are differences of opinion across the members of the scientific advisory panel and I suppose that it would be a preference that there would be a clear answer one way or the other.

But I think this represents the uncertainty of the nature of what we're investigating here and I think honest evaluations from expert scientists. Turn to Dr. Reaves and see if there's any question or clarification. I don't want to do a roll call here but I do think that we've heard the diversity of opinions.

DR. REAVES: We can't think of any on the spot.

DR. HEERINGA: We can return to this later on.

DR. REAVES: This is an important issue and we may ask that you do that.

DR. HEERINGA: Okay, I don't know how it will be done because I won't draft the initial response to the question but I think there needs to be more than just several people said this, several people said that, we'll have to somehow quantify or clear with regard to specific positions and it may come down to even writing out specific positions.

DR. REAVES: Yes I was keeping a tally and I heard the whole section.

DR. HEERINGA: What's the score?

DR. REAVES: I don't know how to score to be honest.

DR. HEERINGA: Please don't score.

DR. REAVES: Some of us may just chat at the next break.

DR. HEERINGA: That would be fine, that would be fine.

At this point, Dr. Chambers, I have mentioned from the beginning of the session to the panel members

that if there were any other scientific issues they feel were not clarified in our response to the charge questions or relevant questions that they would like to introduce, that they would have that opportunity, so Dr. Chambers if you would like to, I'll read Dr. Chambers question and this has...

She submitted this to me as a panel member, this is an additional question on human health related to the question one topic, on the basis of the science that RBC and cholinesterase preparable to brain acetylcholinesterase at the end point upon which to base the risk assessment. That's her question.

Shall I read it again?

On the basis of science is the red blood cell acetylcholinesterase measures I presume in addition preferable to brain acetylcholinesterase as the end point upon which to base the risk assessment. I think we've answered that question to an extent but Dr. Reed?

DR. REED: Could we take that up so that people..

DR. HEERINGA: Maybe if you just put it in an empty color plain slide for us. While they're putting up the question so that everybody is absolutely clear about the question that Dr. Chambers has introduced....go ahead I'll ask Dr. Chambers I'll ask

her to answer her own question.

DR. CHAMBERS: This is the scientific advisory panel and I just feel like there's some science issues here that we've sort of addressed off and on in the other questions but I think that this is important enough at least in my mind to bear a discreet discussion and discreet part in the report, so the question is red blood cell versus brain and I do understand that in the process of risk assessment that you have to be conservative to be protected.

But, I also think that should be based on scientific principles and I have a concern that some of the science has been lost in this decision. Red blood cell cholinesterase may display greater sensitivity than brain acetylcholinesterase in in vivo experiments.

That's not surprising that this might happen due to the toxicokinetic considerations that I brought up earlier. However, the red blood cell acetylcholinesterase inhibition is only a marker of exposure not a request and therefore does not reflect toxicity quantitatively.

It does not seem reasonable from a scientific standpoint to me anyway to base the risk assessment calculations on a biomarker exposure and not a biomarker that reflects toxicity. The experiments

provide reliable and robust brain acetylcholinesterase data. The rationale of greater sensitivity for the choice of red blood acetylcholinesterase inhibition as the end point does not seem reasonable from a toxicological standpoint.

There may be numerous parameters in the organisms that are highly sensitive to inhibition or change if developing from carbofuran exposure but that do not reflect toxicity end points and it concerns me greatly that the risk assessment is based on a biomarker that is not an index of some sort of toxicity.

It should be borne in mind that brain acetylcholinesterase inhibition is really just a biomarker as well. It does not reflect the toxicity as such. It's only if you get enough acetylcholine built up that you're going to start affecting cholinergic pathways. The motor activity changes appeared to be more consistent with brain than with red blood cell acetylcholinesterase and those experiments are ORD experiments.

In addition the choice of red blood cell acetylcholinesterase inhibition is not consistent with the approach used and justified based on toxicity and methocarbanate cumulative risk assessment. That was

mentioned earlier. Therefore I'm urging EPA to seriously reconsider the use of red blood cell acetylcholinesterase as the end point in the risk assessment and to consider using the brain which is a better reflection of toxic endpoints.

DR. HEERINGA: Dr. Chambers' comments, are there any additional comments?

DR. SCHLENK: Brief comment, just I totally support that recommendation. Dan Schlenk.

DR. KEHRER: Steven, may I make a brief comment?

DR. HEERINGA: You sure may, matter of fact I didn't even recognize your voice, I thought somebody was speaking out of turn in the back of the room. Please go ahead.

DR. KEHRER: I think Dr. Chambers hit it right on the head with regards to the brain cholinesterase being the target of toxicity or a more direct reading of toxicity. Obviously we've spent a lot of time discussing the reliability of the brain versus the RBC cholinesterase measurements and the issues involved in measuring both of these on time and laboratory procedures.

So I just want to mention or throw out one caution here in that not see the human data which I

would think would have some measurements of RBC cholinesterase data in them.

Obviously you cannot do invasive brain measurements of cholinesterase in humans that in turn the animal data, the animal RBC data may become useful down the line when we go back to extrapolate the human data if that's going to be considered, back to the animal data so I would just say a word of caution that perhaps we cannot at this point completely dismiss the animal data as not being useful so I'll leave it at that.

DR. HEERINGA: Dr. Brimijoin.

DR. BRIMIJOIN: So I agree totally with Dr. Chambers with the proviso that when we have the valid human data available to us that will come most likely only in the form of RBC inhibition and in that case I would be very reluctant to ignore that data on the basis of it not being a direct measure of toxicity or in effect but I think it would then have a valuable role as a biomarker and I would also say that if we had strong data on human RBC inhibition that would be appropriate to compare that with a similar measure in experimental animal species but that's not the case.

DR. HEERINGA: Dr. Kehrer?

SPEAKER: Yeah, I just certainly think

that as a general matter brain measurements are preferable, both because they're closer to the site of action or the mini site of action and because of their greater reliability.

On the other hand I don't think it's outrageous for EPA to have considered the blood as another compartment that could be predictive of other critical motor system receptors. It has some face validity to it although certainly I think that it's not desirable to put it at the center of the key calculation determining the management action. I think it would be better to go back to the brain basis for the reason.

DR. HEERINGA: Dr. Kehrer:

DR. KEHRER: Jim Kehrer. I'm going to fully support Dr. Chambers. To me the logic of using a marker of exposure to set toxic exposure limits does not exist. Secondly people raise the point of possibly using the rat red blood cell data if human red blood cell data should become available but the two of them are quite different basil levels of activity and they aren't really the same enzyme and so those comparisons could be very problematic

DR. HEERINGA: Dr. Reed?

DR. REED: As I stated before I wish we

have all the information that we have we might have not...not having, for example, the peripheral acetylcholinesterase data I do support the Agency cholinesterase policy of using RBC cholinesterase inhibition as an end point, not so much as a biomarker of exposure but I think as the policy stated is a surrogate of toxicity at the peripheral level and I fully supported that, I felt that information that I presented earlier or mentioned earlier about mouth smacking and chewing motions.

I have no assurance that it's coming from or it's a manifestation of the brain cholinesterase inhibition and so if we know that there is a possibility of some peripheral effect I would say that the brain acetylcholinesterase would not be a superior surrogate now for the peripheral or more preferable than the RBC cholinesterase inhibition so all that I'm saying is that there's something that we don't have data for, it's not the most ideal to use the surrogate but I certainly don't think brain cholinesterase inhibition is only a marker of exposure in the sense of no toxicity relevance so that's my support for the EPA cholinesterase policy.

Just I think all of us are aware of the long many, many iterations of discussion about use of

various cholinesterase inhibition, I mean cholinesterase inhibition at different sites for risk assessment and just as a piece of information different agencies from different groups to look at that policy and possibly, you know, revised many times and I certainly, you know, with the new information that comes available as we go along, I certainly think that this issue can be revisited under that holistic discussion about the policy itself, but our group had also requiring one source of data review and what's available and we came to actually the same conclusion and it's the EPA policy that the RBC cholinesterase inhibition can be used for risk assessment and not just as a biomarker of exposure.

DR, HEERINGA: Dr. Lowit:

DR. LOWIT: It's worth adding to that, thank you, Dr. Reed, that we're not inconsistent with other, not only the county DBR but other federal and state organizations around the world in the way that we use this data.

DR. LOWIT: Is it possible that I could add a comment to that?

DR. HEERINGA: Is it clarifying, I haven't heard, I guess I'll turn to Dr. Lowit...responses aren't part of the discourse at this

point unless Dr. Lowit you feel that was there a specific question that was asked or this ... I'm going to ask

DR. LOWIT: We're in the process of getting a copy of the SAP report from a number of years ago where the SAP actually reviewed our cholinesterase policy just to sort of pull out some clips from that and if that would be allowed.

DR. HEERINGA: If you circulate it I think that. Dr. Reaves and Dr. Brimijoin.

DR. REAVES: I should mention and now I see Dr. Moser, I should mention that I did talk to Dr. Moser about what might be the target cholinesterase inhibition for mouth smacking free motions.

DR. HEERINGA: Why don't you put that question to her and then she can respond.

DR. REAVES: Let me see am I correct to think that mouth smacking and chewing motions could come from peripheral nervous system response.

DR. MOSER: Thank you, this is Ginger Moser with the EPA ORD. There are studies that show that many of the effects of the cholinesterase inhibition can be mediated peripherally and the fasciculation, the mouth smacking that she's referring to are include, are included in those effects.

There are studies that have given both scopolamine and methylscopolamine, one of which gets into the brain, one which doesn't and so you would be able to block the effects of the, parts of the cholinesterase inhibitors either just peripherally or both peripherally and centrally.

And when you block the central effects you still see many of the effects of these chemicals including fasciculation, including salivation and micromation, many of the things that we considered to be cholinergic crisis types of toxicity- salivation, micromation, urination, diarrhea, that sort of thing so these are all peripherally mediated effects and also just to mention that he said these have been done with cholinesterase inhibitors both carbonic and organophosphate.

And, in fact, there are some organophosphates that do not even exhibit brain cholinesterase and yet they produce full cholinergic crisis in which case obviously the red blood cell is the cholinesterase that would have to be used for any sort of risk assessment or evaluation so I think that in these cases one needs to look at both end points instead of just one or the other and look at it at a more independent case by case basis.

DR. HEERINGA: Okay just to be clear where I'm coming from, we will have responses to the specific items but it's not a point in time in this program for additional discourse or debate so thank you very much though, I appreciate that.

At this point in time I think that I would like to move on to the second of the charge questions and...pardon me for the delay. Dr. Reaves.

DR. REAVES: Question number two Point of Departure PoD Determination for Dermal Risk Assessment for Workers. In the 2006 and 2007 human health risk assessment for carbofuran, the Agency has relied on oral studies in adult rats for deriving the point of departure for dermal risk assessment for workers. The Agency applied a dermal absorption factor of six percent to extrapolate from the oral route to the dermal route. The Agency acknowledges the uncertainties associated with route to route extrapolation.

In 2007 FMC submitted a twenty one day dermal rat toxicity study MRID 47143702 that also included a seven day range finding study MRID 47143701. In these studies carbofuran at various doses was applied to shaved skin for six hours per day, five days per week with the skin occluded after application. These

studies failed to provide measurements to address time of onset, time of peak or time to recovery information necessary for the dermal risk assessment.

Furthermore the red blood cell acetylcholinesterase measurements from both studies were unreliable. The Agency has therefore relied on oral studies for assessing dermal risk of carbofuran to workers.

Do you agree with the Agency's conclusion that the dermal toxicity studies in rats MRID 47143701 and 2 are not acceptable for use in extrapolating dermal risk to workers? Please provide a basis for your conclusions

DR. HEERINGA: Dr. Stinchcomb is our lead discussant.

DR. STINCHCOMB: Okay, so the short answer is yes, the assigned reviewers do agree with that . First what we looked at, and this is a group response, what we looked at before even looking at any of the toxicity data as dermal absorption people we always do a calculation based on the Parker and Dye equation which was published in the pharmaceutical research arena in 1992 and is also in a US EPA risk assessment guidance for superfund published documents.

And it bases the human skin cremation of a

chemical on the molecular weight and the log optional water partition coefficient of the chemical and based on the small molecular weight of the compound which is about 221 and the optimal log optional water partition coefficient of 2.32 if you're a transdermal researcher, a lot of people say the optimal partition coefficient is a log of two or same delineation.

We did a calculation from that equation and also using the water solubility from the Syracuse research data base, we got a human skin predictor flux of 1.2 micrograms per centimeters squared per hour so that would be our first estimate before ever looking at the other information so that would be a maximum flux that could occur with human skin and that is a pretty predictive equation.

So then we looked at the rat toxicity studies and we agreed that they shouldn't be used but there were maybe slightly different thinking as to why so we were in general agreement that these are not acceptable for use in extrapolating dermal risk to workers for the following reasons.

The first major point revolves around the lack of certainty of the study end point of six hours as an appropriate time for assessing toxicity. There is no information about the effective exposure time on

the onset peak effect or about the time of effective recovery or the study design presented.

Therefore it is not possible to ascertain that the acetylcholinesterase levels measured in the brain actually are the worst effect that could occur. It is possible that the dermal absorption rate slows substantially after evaporation of the water vehicle early in the six hour exposure so we're talking about during the six hour exposure and not at the end of the study and that the acetylcholinesterase had substantial time for recovery during the exposure period before sacrificing brain analysis occurred.

It was determined that the RBC data could not be used because of the acting methods of the contract lab and that's already been discussed.

The second major area of of concern in those studies is actually in the chemical application method used in the dermal toxicity studies. Regardless of whether or not general guidelines were followed.

In these studies the technical material was applied to the skin of the rats in an aqueous slurry that was then covered with semi inclusive dressing to allow the evaporation of the treatment vehicle. It is possible that after the water evaporated from the skin that the absorption rate of the chemical decreased

significantly.

It is also possible that the small amount of liquid in the slurry was removed from the skin by absorption into the gauze thereby reducing chemical contact with the skin surface.

The particle side of the technical material would also influence absorption rate of the chemical and the particle side is usually not the same size as that in the formulation. The carbofuran product contains multiple components including surfactants which would cause skin formation enhancement, better surface contact and also potentially a longer duration of significant absorption as compared to the technical material exposure in a slurry of water.

Without further information about the effects of an application method using the technical material in a powdered slurry for a six hour exposure there is a significant potential that the neurol recommended by FMC at 15 milligrams per kilograms per day for adults rats is too high to ensure protection of human health from dermal exposure to the carbofuran product in actual use. So that's what's we thought of the rat toxicity studies.

As dermal absorption scientists we've also been recommended a review of the guidelines, the EPA

acute dermal toxicity and the 21,28 day dermal toxicity guidelines and we revisited for improvement of clarity. The vehicle section in particular needs to explain how the product be applied to a specific method but it's similar to how it would be applied in the field which should include using actual products and not just the technical material alone unless the technical material alone can be shown to have equivalent or more toxicity than from the same amount of active ingredient applied to the skin in the at use formulation.

Additionally the procedure for the application of the substance and the covering with four sides should be reviewed.

Application duration and time course of peak effects should also be reviewed in the guideline and may also be helpful for the Agency to review the dermal absorption guidelines simultaneously as these documents also contain similar types of recommendation and scientific methodoly.

So then we thought about the use of the oral toxicities studies and with the lack of other experimental data optimally or properly defined dermal toxicity study it is reasonable to consider cautiously an estimate of dermal toxicity based on oral toxicity measurements with a reliable maximal effect end point

combined with an estimate of dermal absorption. Although dermal absorption results from a previously published study are available the Shaw study, the conditions in that study do not correspond directly to the six hour exposure or anticipated exposed doses. And that in our mind should be on the basis of first skin absorption area.

So these doses are not relevant to worker exposure risk assessment. The six percent absorption values by the Agency is based on 5.7 percent absorption reported from a 24 hour exposure between the applied dose of 63 micrograms per centimeter squared per day so that's a calculation from the 285 minimal dose that the number was used.

Shaw, et al. also presented dermal absorption measurement at two percent for the same exposed dose after six hours of exposure. The Agency recommended using a 24 hour number on the basis that carbofuran in the skin but not yet absorbed systemically at the end of six hours will continue to absorb even if chemical had been removed from the skin surface.

While this is true, the absorption rate from chemical residue in the skin at the end of the exposure would be smaller than the rate while the chemical was still in the skin. Almost certainly then most of the

significant absorption will have probably taken place within the six hour period.

So as far as the use of the amount if you assume the two percent absorption likely underestimates absorption because the exposed doses to the skin are likely to be much smaller than 63 microgram per centimeters squared so the justification for that is often the percent absorption increases with decreasing amount applied especially on small amounts applied and this was actually observed in the same Shaw study of carbofuran although unfortunately the study authors only reported the effect of the dose of 72 hours you can still see that trend which is common in this type of study.

For this reason dermal risk assessments need to consider the amount of chemical per skin surface area in addition to the amount of chemical for body mass. If the exposure rate based on the mixing loading of liquids for aerial applications scenario is approximately 2000 micrograms per day is the calculation we came up with, based on the age ETF data base at the 1.6 microgram per pound active ingredient times 1200 pounds active ingredient applied per day so that's how we came up with the 2000 micrograms per day as an exposure.

Then the dermal applied dose can range from .22 micrograms per centimeter squared per day, that's based on our surface area estimates of a thousand square centimeters for the hands as the smallest exposure and 17000 square centimeters if the entire body surface area of a 70 kilogram person is exposed.

And then we even did a calculation if the unit of exposure is as high as a CHED value of 8.6 micrograms per pound then the dermal exposure could be as high as ten micrograms per centimeters squared per day so these exposure per unit area are less than the six percent number that's being used.

So therefore the percent absorbed goes to be more than two percent in the field exposure scenario and even more than the six percent. In fact there was a number in the publication citing 80 percent absorption at smaller doses; however, it is not known how much higher that percent should be, there's not enough data to tell.

Furthermore the other worker exposure scenarios would have smaller exposed doses than the mixer handler who has the maximum exposure with an increased likelihood with the appropriate percent absorption number would be larger than two percent in those cases as well because the surface area exposure

is actually less so the percentage absorbed is higher.

And we also thought about the dermal absorption rate so the time for the dermal absorption relative to the toxicity response is unknown . In a calculation of internal dose were given exposure for example a hundred square centimeters for the exposure dose of the 63 micrograms per centimeters squared Shaw value multiplied by a percent absorption number for example the two percent for a six hour exposure.

It is assumed that the absorption is a 126 micrograms and it is assumed that that occurred to the single oral dose if you use the oral dosing model. In fact absorption occurred over the entire six hours although not necessarily at a constant rate. As the result at any given time during exposure the actual internal dose will be smaller than the estimated using a percent absorption for the exposed period.

This is particularly the case for a chemical like carbofuran that is eliminated quickly. For example the shots that EPA described at 75 percent of the absorbed dose had already been eliminated in the urine at the end of six hours.

And then we also have a concern about the lack of addressing the oral bioavailability of carbofuran for using the extrapolation from oral study

haven't taken this into account so the percent absorption factor relates the internal dose that arises, the absorbed dose, from a given dermal exposed dose.

If the oral dosing extrapolation is used then the oral bioavailability of carbofuran needs to be included in the MOE calculation with just the oral PoD dose versus systemic for internal exposure Additional the possibility of active metabolite formation needs to have been considered as well so because of the liver you have different considerations there.

So if your oral bioavailability of carbofuran is 100 percent then there's no issue but if it's one percent you have a serious estimation problem.

Then we also felt it necessary to comment on the acetone discussion that was brought up. Although acetone was used to the Shaw absorption study we now decide that the scan is only 200 micoliters on a area of 5.6 centimeters squared This amount of acetone evaporates very quickly and serves only to deposit the chemical into the surface of the skin with with a short evaporation time.

Acetone has little effect if any effect on the amounts absorbed except perhaps in the first few minutes. Acetone effects on the skin are more

problematic when the skin is exposed to acetone for an extended period of time. And I think that summarizes everything we assessed.

DR. HEERINGA: Thank you very much Dr. Stinchcomb.

Dr. Bunge

DR. BUNGE: Okay pretty much everything that I had to say has been covered by the statements that have already been read. I would like to just reiterate that we are concerned that information on the exposure times is not provided in the FMC dermal risk studies or was not investigated and this combined with the effect of the methodology using applied active ingredient has led us to conclude that the FMC dermal toxicity studies cannot be used to lively identify a no effect level.

So we're in agreement to the conclusion of the Agency but not quite necessarily for the same reason. I do want to make a couple other observations. One of these is that I was greatly distressed by inaccuracies in the reporting by the Agency of the dermal toxicity study protocols. And unfortunately when these sorts of errors are made, it encourages distrust of other information that the Agency provides.

It's just extremely important that the Agency

have the facts correct and report them correctly at all times but of course particularly decisions such as the one we're considering here regarding the notification and intent to cancel. The errors in saying that the exposure in the dermal toxicity study was five days per week rather than the correct number of seven days per week and whether there was or was not a one hour delay in sample collection were corrected in the statements made today.

However, I'll say in today's statements there was a new error and that is that the, on slide seven that the motor activity and FOB were conducted prior to the exposure and that was correct but what was incorrect was on day 21, it actually occurred on day 20. It doesn't fundamentally change the conclusion, but it continues to make us, at least myself, concerned that I have to be careful to recheck all facts .

I want to also just reiterate that we would encourage the Agency to view including external scientific review all of the dermal study guidelines and most particularly the toxicity guidelines. So as not to discuss the issues of dose based on surface area in discussing toxicity or the recognition of the effect of the vehicle on dermal absorption.

I should say that the dermal absorption

studies do address these at least to some extent more than is done in the toxicity studies but it still would be useful for all three to be reviewed.

These issues of dose based on surface area and the recognition of vehicle effect have been raised with the Agency before and particularly with respect to the surface area issue, it stated in the documents that we received here specifically the HSRB review of the dermal tox human data, one of the concerns of the data was it was deficient because the exposures of the subjects in the experiment, which was study one did not correspond to exposures likely to be seen among the workers.

And, in particular large amounts of carbofuran in that study were applied to relatively small skin surface and as we've already said here and they said there this is a deficiency in these sorts of studies that's, that's real.

DR. HEERINGA: Thank you very much, Dr. Bunge. We're playing a little musical chairs here because of the human data issue and again apologies to Dr. Brimijoin and Dr Chambers, I slipped them in and out so to discussants again we have heard that it's appropriate to discuss that data with you so just give us a flag that you're going to do it.

DR. BUNGE: I didn't mean it to be discussing the data but simply to say that the deficiency hasn't been pointed out before.

DR. HEERINGA: No, I think that.

DR. BUNGE: And in other documents as well I just didn't have the other one at my fingertips.

DR. HEERINGA: No problem at all. Dr. Lu the next associate.

DR. LU: I have nothing to add.

DR. HEERINGA: Let me open it up at this point in time we have had a very thorough review and presentation by Dr. Sinchcomb and Dr. Bunge, any additional comments on the application of the dermal risk dermal toxicity studies in rats?

Okay, I'd like to turn then to Dr. Reaves on question two whether you have, again if there are any questions of clarification of the panel and then the statements that were made.

DR. REAVES: On question two I think we're good.

DR. HEERINGA: Okay what I'd like to do at this point I don't want to have a full lunch break because I think that there are people that I anticipate that we only have an hour left in our proceedings but I'd like to call about a fifteen minute break and if we

could come back at ten minutes after twelve I would hope to proceed.

There are some remaining issues to discuss. I think that the EPA staff wanted a little time to consider the issues on the question number one and we have a few things to revisit on the ecological risk assessment from yesterday so let's, we'll break now until ten minutes after twelve and then we'll reconvene.

(WHEREUPON, a lunch break was taken.)

DR. HEERINGA: Well, welcome back everyone to the wrap up of our multiple day session of the FIFRA Science Advisory Panel, on the Notice of Intent to Cancel Carbofuran. At this point in time, we have completed an initial pass through the charge questions and because of again the broad and very serious nature of the meeting here, I wanted to make sure that we have full coverage of all of the scientific issues which is the real and responsibility of the SAP.

I'd like to return to the ecological and avian risk assessment that we addressed primarily yesterday in our charge questions and in response to a written comment I feel that I want to reaffirm the panel's response to charge question number five and if

I could again have Dr. Odenkirchen read charge question five for the panel. Use both mikes.

DR. ODENKIRCHEN: Charge question five. Having read the EPA presentations and public comments on EPA's proposed action has the information provided in this meeting taken as a whole caused the panel to reach conclusion contrary to EPA's assessment that carbofuran poses a significant risk to mortality to numerous avian species in locations where carbofuran is used. If so, please provide the basis for that conclusion.

DR. HEERINGA: And it's always of course important to focus on the adjectives in these questions and Dr. Montgomery if you would...

DR. MONTGOMERY: If I could just read the final conclusion in the response that I made yesterday to this. The final conclusion after going through the three lines of evidence, and looking at charge questions under each of those three lines of evidence, what we concluded, does the conclusion of the SAP and much of the discussion centered around data quality issues and concerns the study design had a variety of design features that introduced uncertainly as to the utility of the data.

It was also concerns expressed by several

panel members of various points and discussions that studies and models were developed independently and not part of a public for peer review process.

Using multiple lines of evidence to determine its risk assessment probabilistic risk assessment incorporating the data wildlife mortality questions and field studies with the information provided prior to and during the SAP meeting the panel has not reached a conclusion contrary to the EPA's assessment that carbofuran poses a significant risk of mortality, numerous agents even species and locations where it is used but that the probabilistic modeling is a useful tool but models are only models and we need to verify operating parameters and assumptions with actual field data. That was the conclusion of the response that we made yesterday.

So I think the answer to the question is that the panel feels that they've answered the charge and that in the charge question as presented to us there's no change in that conclusion, however, having said that in its high level component that I made a request before receiving this question from FMC this morning, the other panel members receiving it, I did want to make an additional comment if I may.

DR. HEERINGA: You certainly may right

now.

DR. MONTGOMERY: At a time appropriate, this is appropriate, if you'd rather I wait.

DR. HEERINGA: Yes, please go right ahead.

DR. MONTGOMERY: Okay, this is a personal comment but it's also in part integrating responses from other panel members that we've had, some of our discussions during the week, some of them yesterday evening, after we had wrapped up the ecological portion of the panel meeting and other people here will, you know, kindly remind them to clarify or provide the nuances that they feel are important.

My personal comment correlates, the result comes as a function of use pattern and the resulting residues and when I say residues I'm combining exposure into this. It's a technical comment, I understand that we are not here to evaluate whether or not a label was appropriate, we're not here to evaluate economic applications or performance efficacy, and we're not here to look at cost benefits but I think this is a technical comment that generalizes independent of any of these other assets.

It goes to use patterns of this product that

include from the label I read furrow in-band and foliar, which is by ground rule. We agree in the meeting that we felt residues would vary within the field and variation can come in sort of two categories, I think.

One is the kind of variation that you might see if you have a foliar application which could cause variation due to canapy or woodchuck of the machinery moving through the crop, it could be humidity, it could be temperature differences, you know, those kinds of factors and that is I think a different type of variation that comes from an application like bandit or inferral where you see variation residues because the product is applied specifically in a location as opposed to broadly over a field and I think this could result in localized residues and this comment is brought forward, I've thought a bit more about it.

There was one public comment made yesterday and it is the comment that was made by Michael Horall from Melon Acres, I apologize if I pronounced his name incorrectly. He showed us a slide on page six that showed tunnels over cucumber seedlings that they use to protect them from cold weather promote early growth and he said that the tunnels prevented...

They applied and put these tunnels over

it...and it seems hard for me to believe that this use pattern could result in the same type of avian exposure as some of the other use patterns we've seen so having set the stage on this and leaving as I say the other factors that are outside of our purview to do it, I think that the risk assessment as we looked at it dealt with residues in plant exposure in aggregate and we never really looked at residues nor did we have the time to look at residues as a function of application methods.

And I don't know the answer to the question but it seems reasonable in a risk assessment especially one where heavens knows we have so many variables to pick from it hardly seems that it would be difficult to change one variable a little bit by sub-dividing the data set to reflect residues that result from use patterns to see if this affects risk conclusions and I know that other panels every panel....other panel members have opinions and views on this and I'll turn it over to them to let them elaborate on any issues they'd like to make.

DR. HEERINGA: And I think too to focus on the element of the question of significant risk in birds in locations where carbofurans...

DR. MONTGOMERY: If I could just add

just a little trailer on the end of that.

DR. HEERINGA: Sure.

DR. MONTGOMERY: Is that to conclude this end when I talk about the level of exposure to the level of risk that I'm wondering if it's possible and I think that it's important that our science represent field conditions as much as it can, the conclusion it's come to would all of these use patterns and residue thrush pose resulting from the resulting significant risk.

DR. HEERINGA: Dr. Odenkirchen

DR. ODENKIRCHEN: Setting aside the adjective significant because I think we all have sort of a comfort issue with regard to whether that's a term of art or a term of science or a term of mathematics but let's deal with what we talked about the risk levels.

There are three sets of tables within the I-reg, I think there are 3.12, 13 and 14 that present the risk results for corn, corn folier, corn in furrow bed, etcetera and then for alfalfa folier so we have accounted for the effects of application as it relates to in furrow and bandit applications.

How we dealt with a very highly specific use pattern that involves covering crop with some, with

polyethylene or with a tunnel and the answer to that would be no but we have incorporated the application method as it's related to folier ground boom in furrow and bandit.

DR. HEERINGA: Dr. Montgomery.

DR. MONTGOMERY: I guess I wasn't a completely complete in that in this idea of applications is also the idea of mitigation because part of risk assessment is not just exposure but also mitigation so I apologize I hadn't included that in the first response.

DR. HEERINGA: Dr. Grue

DR. GRUE: Yes maybe I could just add a little bit to this, for me the inclusion of the adjective significant in question number five versus question number one created some problems for me and whereas it is much more easier for me to answer question number one, it was much more difficult to question number five because of that adjective and what I want to just enforce here.

And I think Cheryl captured it and I'm confident ultimately of our response the written response to question five was incorporated was that one residues do not equal exposure, the scenario in which those residues exist and the species that are there,

their behavior, I mean we discussed all of those during the course of the meeting.

The second, the other point is that for us to define significant when the Agency and this was the question that was posed at the end I believe of our discussion of question five, at the Agency how did you define significant I believe the registrant did make an attempt to define significant, is problematic I think for us, that was not that becomes a policy decision versus the science decision and that's where I personally found it very difficult to more difficult than to answer number five than number one and I think you know that Cheryl captured this and I would encourage other panel members on the eco group or whatever to comment on that as well.

DR. HEERINGA: Dr. McCarty I think.

DR. MCCARTY: Again my personal views on this. I in my approach and in my discussions with people what I saw us doing and this is pertaining to question five was evaluating the science that went into determining the magnitude of risk that was then used by EPA to quote make the assessment that carbofuran poses a significant risk in mortality, etcetera, etcetera, etcetera now where exactly quotes and commas etcetera to that fit in there I'm sure lawyers would have an

opinion about that, I'm not a lawyer, I'm just saying how I approached it.

Now, significant even talking about significance and I talked about significance yesterday but at least I hope I tried not to say I knew what was significant and the reason is that's not a science question in my opinion.

That is a policy question. If the policy tells us here's your definition of significance risk quotient greater than one, science can inform that decision we can try to estimate the magnitude and say yes or no but making the decision of where to cut off a significant lines is and I'm trying to be precise here so pardon my pauses, you know ideally that is answered by the American people who we're here to serve.

It's not answered by a group of scientists, it's not answered by the registrant. I can think of a range of definitions of significant is one bird chilled in violation of the Migratory Bird Treaty Act, a significant risk or are we going to make the policy decision that we need to show that enough mortality is occurring to drive a population to the threatening and endangered species level.

Those are policy decisions, not science decisions. If they give us those decisions we could

inform them so we talked about significance but that to me is not question we are here to answer and we're not here to define significance

DR. HEERINGA: Thank you Dr. McCarty. Dr. Clark.

DR. CLARK: We had discussed this yesterday and I think it does get to the issue of...we were struggling just to quantify the magnitude and I...and we listed a variety of reasons why we thought that there was uncertainty in terms of the magnitude of it and the essence and mortality and I agree with what's been said in terms of if it's a simple question is there a risk of mortality and the simple answer to that is yes.

When we do into defining what the cut off level of where magnitude becomes significant and I think we all are human here, that really is a policy decision, very difficult for us to answer that as it stands.

DR. HEERINGA: Dr. DeLorme.

DR. DELORME: Well I guess I was the one that opened this can of worms up because I was the one that struggled with the word significant. Just a couple things and trying to get my thoughts together here.

As I re-read the question here the way it's worded is EPA has already made a determination of significant risk okay so they obviously have sort of mechanism of determining what constitutes significant risk and as Cheryl pointed out you know from a scientific perspective we are asked to determine whether or not we had reached a conclusion contrary to EPA and her answer had indicated that no based on the science we hadn't, but added to this I think that her comments with respect to the model is that they are models and I think I had commented earlier that they are models and we have to recognize that when we're looking at the outputs and the conclusions of some models.

And I think also that I had indicated yesterday that I don't think there's any doubt that there is there is room for a mortality from carbofuran or avian but risk is probability by definition so the probability of an event is really I think we can have magnitude events with large effects based on the assessments and the probability or the frequency I think is open for debate at times and that's what we were trying to make the models to conform as and there is a range of probabilities of a large magnitude of things happening.

DR. HEERINGA: Dr. Sample.

DR. SAMPLE: I think most I concur with the discussants being made also recognizing that Dr. Montgomery had brought up with the issue of this exposure scenario recognizing that is a critical factor, risk is a function of exposure if you don't have exposure there can be no risk so in there are constraints that we approached the question by and the scenarios by which the models were run but I think it is important to bring out the point and recognized that if there are use scenarios that the management and policy issues that there would be changes in the conclusions depending upon what management scenarios were to be evaluated.

DR. HEERINGA: Dr. Sparling and Dr. Grue.

DR. SPARLING: I pretty much think we're in unison with regards to trying to assess risk and what the significance of it is. The studies that we were asked to evaluate going back to Jorgenson and the other studies I don't think any of those studies were rigorous enough to be able to test risk in a population level.

That is a very tricky thing to do and I think that a much more rigorous test would be able to get us

better information on level of risk. Those studies clearly show that there was a risk, we know that there was a risk in individuals, it's up to the EPA again as I agree with everybody else to define whether population risk is what we need to assess.

DR. HEERINGA: Dr. Grue.

DR. GRUE: Maybe just one other point and this is personal opinion here but we were not asked to assess whether or not I don't believe we were whether or not we felt that the existing risk, however that's defined and quantified, could be mitigated.

Now that was not in our charge and I want to make sure that if in fact that's the way other panel members feel that is not...that our response to question number five and I think I want to make sure that's the whole panel feels, that's incorporated in there. That we are not commenting on the potential for mitigation of the risks that have been expressed during our discussions here over the last week.

DR. HEERINGA: Dr. Montgomery, would you like to wrap it up.

DR. MONTGOMERY: I have to agree with that and support it. I think that one aspect that the activities that we did this week did not have what we would normally have in a risk assessment is the

application of scenarios, a range of reasonably expected scenarios and how that would affect risk.

We normally do that when we are putting a risk assessment together so the charges as it was given to us was quite focused and didn't ask us to consider if you know you if the use pattern resulted in a different exposure what might happen to it so I'd have to agree with you that our charge was quite narrowly defined and insofar as that charge, we haven't changed the conclusions in the other response, the final response to charge question five.

DR. HEERINGA: Thank you very much and at this point I'd like to turn to the panelists and the entire panel is obviously engaged in this process but we do divide a bit by specialties and expertise and it's quite apparent but within the ecological risks section any of the charge questions any additional scientific matters of import that you think should be addressed or commented on. Dr. DeLorme?

DR. DELORME: One of the issues that came out here was the need for better data on field use by birds. As a suggestion and personal suggestion but taking a page out of our colleagues on the other side of the table here in the human health.

It seems to me that on the human health side

of the equation they often form task forces to put together data that's usually agreed upon, the use of risk assessments. I think with respect to the issue of bird use appeal EPA may want to look at this, there's data out there, I think we all know that it's out there, it's just a matter of getting it, getting it together and analyzing it because I think that would really really help us in clarifying what's going on and how it can be used.

DR. HEERINGA: Dr. Montgomery.

DR. MONTGOMERY: I'll just tack an addendum onto that. I think that in addition to the field data the....I honestly can't remember what day I said this, but I think that it really is useful to see how much data we can pool because we are moving into a stage where we're now doing probabilistic and the more data we have it's just impossible for a registrant to generate all the specific data they need to make one of these models run and anything close to an acceptable manner but as we said the combining of this data is very tricky and will always be kind of a bone of contention so...

I think that the point is very well made, that has the equivalent to the worker exposure task force and you know these kinds of multiple member if

you want groupings were we can pool our data for this would be really beneficial but more than just previously to the whole as much of this afternoon setting that we can.

DR. HEERINGA: At this point in time I think I would like to switch back to the human race and I think that Dr. Salice, Dr. Odenkirchen, Dr. Panger for reappearing and joining us. I don't see the human risk people here yet. Are they within ear shot. We need a few more minutes so just at ease, I guess. I'll let you know when we're ready to recommence. Don't go far though.

(WHEREUPON, there was a pause in the proceedings.)

DR. HEERINGA: Okay, if everybody, it looks like nobody left, we just need a designated federal official and members of our panel, okay, very good. I would like to return then to I guess wrap up our charge questions at this point, and any additional comments on scientific issues that we feel are relevant to the human health risk assessment or component of the presentations in our review. And I guess I will turn to Dr. Lowit first, or Dr. Housenger.

DR. HOUSENGER: Yeah, we thought about coming back up and asking a clarifying question, and seeking other guidance from the panel, but I think the

dissensions, that kind of emphasize the difficulty with this issue that we had as well. And our only request is that the final report reflect all of the opinions and characterize it as not having a majority opinion as far as we can tell, of any one recommended path.

DR. HEERINGA: We will commit as a panel to represent the diversity of views and the appropriate weight on the diversity of views within the panel. At this time I would like to turn to the panel to see if there are any other follow up comments, general comments, or introduction of comments on scientifically relevant material that may not have been under the scope of the charge question. I think Dr Portier.

DR. PORTIER: Thank you, I wanted to return to the FQPA issue, because as you said, it's a very, kind of important, it's an important discussion and at the break I had a opportunity to talk to Dr. Brimijoin and Dr. Reed, and really kind of clarify whether there is a kind of a diversity of opinion here, or we were kind of saying the same thing from multiple directions.

I am going to read something that I have written here, and I am hoping that they are going to

sit down and say "yeah that's right, and that's right". But I think we actually were trying to say the same thing. FQPA requires EPA to apply a 10 X safety factor for infants and children in dealing with POB. Without other reliable data, this 10 X safety factor would be applied to the adult rat B D 10 level.

The discussion of the panel seems to indicate that the rat in the 11 level, or BC data are not reliable, and hence using the ratio to establish the use of a 5 X safety factor applied to the B & D level in the 11th rate level should not be considered. Or another way of putting it, represents a weak argument. Our recommendation from the panel is to simply implement the standard FQPA safety factor applied to the adult rat level.

Now a personal comment, I noted that applying the 10 X FQPA factor, and a 10 X animal to human factor, and a 10 X within human variability factor results in a POB for Carbofuran that's actually 10 X lower than that computed for Albacarb. But Albacarb and Carbofuran are very similar in the NVL thin adult rat values.

So the only reason for the difference in the POB is the lack of human data on Carbofuran. And so the next question that I ask myself is whether the

registrant could in the current research environment ever obtain such human data? And the EPA has to ask itself how is it going to handle this hole in the level of evidence for future chemicals.

So I think this issue of lack of human data for these pesticides; you are just seeing the beginning of this, not the end of it. I suppose monitoring data, epidemiological data might be able to be used to fill that hole, but I don't see it as a statistician, I want to somehow use the information on the other Methyl Carbofurans to kind of inform this decision, shrinkage estimator and shrink that POB closer to Albacarb, but within your legal environment I am not sure that's even, that would be considered a strong enough argument.

So at this point I am going to turn it over to either Dr. Reed or Dr. Brimijoin to confirm or deny that that was our conversation.

DR. HEERINGA: Nu, do you want to?

DR. REED: I think there is many ways to look at this issue and come to perhaps some conclusions, or I should say conclusions might not be as different as reasons behind it.

And my feeling right now about what we are doing in making, giving our opinions about what the

FQPA safety factor should be is really based on the information that we have already seen right now, and as I predicted before, that it's really based on what we were presented with, as Brain and RBC are the most sensitive end-points, and within that, then I do feel comfortable, as I stated before, that this intratendancy of 4 would justify for the uncertainty or the safety factor of 5 X.

And the effects had a range, and if we also present the range that would be 10 X, and that would be the same as what is mandated by FQPA. And I think it is important to retain that picture in our presentation. I am a little bit uneasy about going back to using adult cholinesterase inhibition data, and just essentially not to consider any information that we consider at this meeting and say, "just go ahead and use the default safety factor of 10" and use that as a reason, the reason being that it is unreliable information for us to move away from this, the default of 10. I think we do have some information, but not a complete set of information.

DR. HEERINGA: DR. Brimijoin, I guess.

DR. BRIMIJOIN: Well I guess I would be perfectly comfortable with using the juvenile brain, I'm just reiterating my position, using juvenile brain

data, possibly for the small but not a 5 fold correction for the supposed extra sensitivity at the red cell at that age.

Then simply applying, assuming that that correction accommodates the FQPA factor, and then applying the 10 X to these sheets. I would also be comfortable though with the idea that since we are making inferences, a series of inferences that weaken our confidence, in that approach.

An inference that we should do something to revert to a default mode. Which will get us to a very similar place. And these inferences are: 1) That the RBC data is relevant, is in fact more relevant than brain data, and should be given precedence. 2) That we have accurately measured the extra sensitivity that is supposedly occurring, and I think the central tendency may smaller than, is likely significantly smaller than the 5 fold effect that we were talking about, and as Dr. Reed mentions, there is uncertainty in that.

And I think the uncertainty and the level of difference could not, should not perversely, should not perversely raise the FQPA factor.

So it should require a solution that works toward the default mode. So, in summary, I am uncomfortable with a total five hundred fold correction

as CDS suggested. I could live with either of two arguments for going with a smaller value.

DR. HEERINGA: We have considerable discussion, and I think there are a wide diversity of reviews which you have obviously heard and had a chance to discuss, and we'll see in our report that. . . unless someone has a new position or has changed their mind, I would like to move on to any other issues of scientific import that you feel are relevant to human health risk section, Dr. Hattis.

DR. HATTIS: We didn't get any charge questions on, that were related to the dietary risk exposure in risk assessment. I think that what was in the documents that I read was an aggregate assessment for all current residues, which are based upon all current uses.

And I think clearly as we move forward it's considered both, whether use by use they present an unreasonable risk unique to... clearly a use by use contribution to the dietary residues. Whether each of them in their anticipated volume, because that's also a factor. That's a chance to modify the analysis.

The other minor comment that's on the ecological side I guess, and that is that both, there was a problem in determining the group, a level of

significance in terms of probability of harm, and magnitude of harm that counts as either de minimus or how you actually weigh it in relation to other items of interest.

I know that's the R chart, but clearly I think that's going to be part of the agency's striving to achieve transparency. To define how you take the probabalistic inputs from either dietary or a ecological assessment and transpose them into policy relevant terms under the mandate.

DR. HEERINGA: Dr. Macdonald.

DR. MACDONALD: I'd just like to follow up on something that Dr. Hattis had said. Just before we left for the meeting that we received a rather shocking document about the effects of Carbofuran on cucumbers with extremely high levels of exposure. But I don't recall seeing cucumbers mentioned at any point in this meeting. Is there somebody from the agency there to say what's the status there, is Carbofuran actually used on cucumbers?

DR. HOUSENGER: It is registered under cucumbers, and what we did was we looked at. . . if a child eating a small portion of the cucumber were to get a residue that we saw in the ppb monitoring, it was reported what the apath would be. And that's, I

believe that was in our presentation. Yeah, I think it was represented as that. There is a specific slide that identifies cucumbers as well.

DR. MACDONALD: Dr. MacDonald again, is this in common use for cucumbers, or again is it just an occasional rescue?

DR. HOUSENGER: I think it's a relatively small percent of the crop treated, but 10%, up to 15%. But we did find some tactical residues and ppb models.

DR. HEERINGA: Let me pose one additional question for comment to the panel since it was raised, I think it's relevant. With regard to the ppb data, and use pattern changes over time, do you feel there should be an incorporation of reflection of current use patterns in using current ppb data? I think there is a specific reference with regard to potatoes, is the question that I am at. These are data input questions, and relevant data input questions that I think are important.

DR. HATTIS: Yeah, I think current use patterns should be considered as one proxy for future, or actually the choice of policies effects future residues, and current residues are some sort of a clue as to what that might be. But we should also of course

incorporate what the anticipated changes are, from currently considered policy options.

DR. HEERINGA: My question here I guess is to reinforce that we are considering current uses, and current registered uses. Not future changes, but even under current uses there have been changes, that I think realistically should be reflected in the dietary assessment.

DR. HATTIS: Sure.

DR. HEERINGA: Ken Portier.

DR. PORTIER: Well, I, you know, could use that same argument for the eco-assessment too, with its current Geo/Spatial application that is going to be taken into account. So I'm assuming that the Agency is going to do all that.

That's less of an issue. The bigger issue I found on the eco side is, my concern is, changing crop patterns. Today's agriculture is not tomorrow's agriculture. Probably if the Agency re-registered it, it's registered on corn, thinking, "oh it's a rescue crop on corn" and then corn triples because of the market, which means it's rescuing a heck of a lot more space than it was this year, but I'm sure they are going to worry about that.

DR. HEERINGA: And again, I think our

consideration here is current and recent uses, because of the nature of this risk assessment. Obviously what I thought was a logical step; people tend to agree with it. Dr. Montgomery.

DR. MONTGOMERY: The eco group did talk about that, and you know that considering future uses was not within the charge question that we were given. But there was this uneasiness that what today is mitigation on a small crop is a rescue on the thin edge of the wedge that becomes a rescue of large acreage at some point in the future. Because, as you know, agronomic practices change, so I know it's not within our purview to look at future use.

But you can't have the type of discussion that we have been having amongst ourselves about mitigation, and what that does to exposure without looking - part of the ecological risk paradigm is completed by potentially completed of potentially completed exposure pathways.

And many times we have considered reasonably anticipated future uses, and it's all you know, part of what we've been given to do as part of our risk assessment process, and you have to put boxes around things.

DR. HEERINGA: And I think it's the

nature of this proceeding and this particular meeting, that obviously if we were here in a general discussion about long term strategies it would be different. Dr Sparling.

DR. SPARLING: Don Sparling. I want to reiterate something I eluded to yesterday, and excuse me if it comes at a little bit of a pique, because I am sure the EPA is fully aware of cross ventured ratios. But in the notice to cancel, there are a number of uses for Carbofuran that limited, greatly limited uses, where it was suggested that Carbofuran was the only product that was available for crop protection.

I think we need, I would highly recommend, and I am sure that they will, EPA examine where Carbofuran is the only product at this time. Or where taking to an alternative could be actually more disastrous in risk, and that's a possibility. Or more financially of a liability at a local level. In the notice of intent to cancel they looked at crop positivity and cost nationwide, and I don't think that's a valid determination of cost.

So, I would encourage the EPA to take a look at whatever their decision is. It they take a look at the mode of cost benefits ratio's now.

DR. HEERINGA: DR. Hattis.

DR. HATTIS: Just a matter of using the models in ways that inform you but don't conclude or mislead you, that there is uncertainty in these models. But part of the uncertainty that is not captured in most models is in fact the uncertainty in the implicit projection of current practices for the future. And that's something you ought to add, at least mentally, perhaps even additionally.

About corn grown, how it's grown, where it's grown, as well as the need to have bigger or smaller refuges of untreated, a corn that's not, doesn't have some of the other complections that are now available. That has to factor, you know, in to your ultimate assembly of facts for the decision maker, and that persons.

DR. HEERINGA: And on that note I think I would like to turn to Dr. Housenger, Dr. Lowit or Dr. Reaves.

DR. BRADBURY: I believe we are all set with human health, and my colleagues behind me I know have received the information that they need for the digesting, the ecological questions. EPA is pleased with all the input that we have received and have understood as best we can, the verbal discussions, the direction that the panel is heading it up, as far as

the agency is concerned.

DR. HEERINGA: Thank you very much. I would like to thank on behalf of the panel, the EPA scientists from both groups, the eco group and the human health group. All of the public commenters and participants, representatives of the registrant. A tremendous amount of information provided in advance during the course of this meeting.

I think it's overwhelming, I know I am going to go home and take a nap. With regard to the panel. I want to say to each of you too, I appreciate not only the expertise that's represented here, but the diligence with which you prepared. I think I always have a little anxiety coming into this that people arrive unprepared.

I looked at the list and I knew that wasn't going to happen this time and it certainly didn't. So again, I very much appreciate all of your participation, and all of your contributions to this process. In a moment I'll turn it over to Dr. Matten, but I would like to, to Dr. Bradbury, I would like to also say that on behalf of the panel we will work with diligence to summarize the proceedings of our comments.

Again to the public, and to the audience, when you read the final report, Dr. Matten will give

you the final details on that, you should not see or hear, or interpret anything there that you didn't hear if you were awake for the 3 and 2/3rds days that we have been at this. So at this point I would like to go back to Dr. Bradbury.

DR. BRADBURY: I just wanted to take a few seconds to thank the panel for all the hard work. We greatly appreciate the time you spent before you got here, as well as the midnight statistical analyses that were apparently turned in by some of you.

It's very much appreciated, and as you all know, it's a very important decision that we need to make, and your review is a very critical component of this decision. We greatly appreciate your efforts, thank you.

DR. HEERINGA: Thank you, Dr. Bradbury. At this point in time I would like to turn the meeting over to Dr. Charlene Matten, who is a designated federal official for this meeting.

DR. MATTEN: Before we close, I have a couple of comments related to the timing of the minutes, and placement of certain documents in the docket. The, as I said on the first day, because of the considerations related to panel deliberations in relationship to the potential notice of intent to

cancel, we have made a determination that the report will be done in 30 calendar days. We have a schedule for that.

All panel members will be meeting next door, because we have almost, will probably have our first draft before they are allowed to leave on the airplane.

The second area is the public docket. As of this morning, or last night, I added and posted all of the Agencies presentations, all of the FMC presentations, replaced hard copies of all the materials that were provided to us throughout the proceedings, including any papers that we had in our possession, any of the slides.

Those will all be made available in the public docket. I think most of those are there, on the 4th floor right now, and those that I have electronically, I'll also try to provide. And if you have anything that you have provided, especially from members of the public, please make sure that I have them before you leave.

Now, coming to the appreciation part of the designated federal official's responsibilities. I wanted to extend my appreciation to the panel members, and their responsiveness to the call to participate.

To the preparations and deliberations of this

panel, and their commitment to following through with the preparation of the report next month. I'd also like to take this opportunity to thank the members of the EPA staff and management for their participation and extensive preparation, as well as members of the public and including FMC and all they help they have been providing me with all the electronic and paper copies in a very timely way, and all the other members of the public that have submitted their written and oral comments.

If there is anything else that you need, I guess you have just a couple of minutes before we adjourn. So if you need something, race right up here before our meeting ends, so that I can put them in the materials for the panel to consider, and for the public to have. And with that, I believe we have had a very successful meeting, and I will turn it back over to Dr. Heeringa to make any last comments.

DR. HEERINGA: Again, my thanks to everybody for their participation this week. It's been a challenging week, but I think also it's instructive, and I think in many ways an interesting process.

I think we have done due diligence to the scientific reviews that we were charged to present here.

So thank you, thank you again for everybody in the audience, the EPA staff and the public, for their part in the process.

At this point then, I am going to call the meeting to a close, and safe travel everyone.

(WHEREUPON, the **MEETING** was adjourned at 1:07 p.m.)

CAPTION

The foregoing matter was taken on the date, and at the time and place set out on the Title page hereof.

It was requested that the matter be taken by the reporter and that the same be reduced to typewritten form.

Further, as relates to depositions, it was agreed by and between counsel and the parties that the reading and signing of the transcript, be and the same is hereby waived.

CERTIFICATE OF REPORTER

COMMONWEALTH OF VIRGINIA

AT LARGE:

I do hereby certify that the witness in the foregoing transcript was taken on the date, and at the time and place set out on the Title page hereof by me after first being duly sworn to testify the truth, the whole truth, and nothing but the truth; and that the said matter was recorded stenographically and mechanically by me and then reduced to typewritten form under my direction, and constitutes a true record of the transcript as taken, all to the best of my skill and ability.

I further certify that the inspection, reading and signing of said deposition were waived by counsel for the respective parties and by the witness.

I certify that I am not a relative or employee of either counsel, and that I am in no way interested financially, directly or indirectly, in this action.

CHARLES DAVID HOFFMAN, COURT REPORTER / NOTARY

SUBMITTED ON FEBRUARY 8, 2008

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