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FIFRA SCIENTIFIC ADVISORY PANEL (SAP)

OPEN MEETING

SCIENTIFIC ISSUES ASSOCIATED WITH THE
AGENCY'S PROPOSED ACTION UNDER FIFRA 6(b)
NOTICE OF INTENT TO CANCEL CARBOFURAN

U.S. ENVIRONMENTAL PROTECTION AGENCY
CONFERENCE CENTER- LOBBY LEVEL
ONE POTOMAC YARD (SOUTH BUILDING)
2777 SOUTH CRYSTAL DRIVE
ARLINGTON, VIRGINIA 22202

FEBRUARY 8, 2008

8:32 A.M.

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

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

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

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

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

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



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

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

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

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

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

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

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

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

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

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

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

18 **DR. HATTIS:** Dale Hattis, Clarke
19 University, mechanistic modeling and uncertainty of
20 variability.

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

25 **DR. BUNGE:** Annette Bunge, from the

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

6 For intra species the Agency is applying a
7 10X for extrapolation of animal to human and unlike
8 FMC's request on Wednesday to rely on the human data
9 the Agency is agreeing with the Human Studies Review
10 Board, their conclusions in 2006, that the oral human
11 study is scientifically deficient so the Agency is not
12 relying on this study to inform the uncertainty factor
13 for carbofuran.

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

25 **DR. HATTIS:** What was the number of

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

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

6 **DR. HATTIS:** Thank you.

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

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

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

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

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

13 Our data derived approach is consistent with
14 the international communities specifically with the
15 2005 IPCS guidance on chemical specific adjustment
16 factors. This guidance is for the use of equally
17 effective doses for example the BMD 10 or the BMD 50
18 and we went through that comparison on Tuesday and as
19 Dr. Setzer explained the BMD 50 there is less
20 uncertainty because we have data around this dose.
21 Unlike the example presented by FMC on Wednesday by Dr.
22 Silkin which was to compare effect at the same dose.
23 And so the Agency has relied on the BMD 50 for data
24 derivation of the FQPA factor instead of the BMD 10
25 because of the lack of red blood cell data at the low

1 end of the dose response curve and therefore

2 uncertainty around that estimate.

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

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

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

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

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

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

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

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

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

7 We would then add on a hundred uncertainty
8 factor for a derivation of .5 milligrams per kilogram.
9 However, if you look at the human dermal study, there
10 is red blood cell cholinesterase in addition at .5 the
11 same level and this was in two subjects and of course
12 we don't have brain to compare from the human studies
13 so it's another point that the red blood cell is
14 important consideration in regulation and either with a
15 10X or a thirty X uncertainty factor that brings you to
16 a much lower dose for regulation so if we consider the
17 human study it would not be protective of human health
18 and we feel that based on the rat dermal study alone is
19 not sufficient for use in regulation.

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

1 again we agree with the Human Studies Review Board in
2 2006 that the study was unethical and scientifically
3 deficient that although it was informative it should
4 not be relied upon for point of departure or for
5 informing uncertain factors in risk assessment.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

18 **DR. BUNGE:** I'll read my joint...Annette
19 Bunge. My question relates to the values that reported
20 just now in your presentation on the human dermal
21 studies. I'm looking at the HSRB report from May of
22 2006. In that report it says neither subject dosed
23 with one or two milligrams per kilogram experienced any
24 symptoms. A dose of four milligrams per kilogram
25 resulted in symptoms which you list on your slide as

1 four two. Is the report incorrect?

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

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

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

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

22 **DR. LICCIONE:** Phase B 1977.

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

25 **DR. LICCIONE:** No, there was one



1 where...

2 **DR. BUNGE:** There was one subject...

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

1 remarkedly similar brain cholinesterase data and when
2 evaluated in combination provide data from low to high
3 doses. However, the Agency identified problems with
4 the red blood cell acetylcholinesterase data from the
5 2007 FMC study.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

25 And with rats and mice it's really quite

1 difficult and I think this present data merely confirms
2 this point without very specialized attention, and a
3 routine laboratory assay is going to have problems with
4 variability and very low signal to noise ratios.

5 Studies involving carbamates have to cope with the
6 further complications of rapid recovery in vitro.

7 Since the rate constants for regeneration of
8 N-methyl carbamate enzyme allow fifty percent recovery
9 in less than an hour, about forty minutes in my lab.

10 All these problems appear to have been operating in the
11 sponsor studies on inhibition of RBC cholinesterase by
12 carbofuran.

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

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

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

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

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

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

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

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

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

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

1 it over to the other.

2 **DR. HEERINGA:** Okay Dr. Brimijoin. Dr.
3 Chambers.

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

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

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

25 Red blood cell acetylcholinesterase is viewed

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

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

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

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

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

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

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

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

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

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

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

25 Therefore it does not seem reasonable to me

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

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

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

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

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

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

4 **DR. HEERINGA:** Dr. Reed.

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

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

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

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

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

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

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

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

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

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

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

24 **DR. HEERINGA:** That's fine.

25 **DR. EDLER:** The first thing is I think

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

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

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

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

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

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

16 **DR. HEERINGA:** Dr. Hattis.

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

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

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

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

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

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

15 **DR. HATTIS:** I just wanted to thank Dr.
16 Chambers.

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

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

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

12 **DR. HEERINGA:** Dr. Reed

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

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

25 **DR. REAVES:** Question 1B, the

1 exponential dose time response model used by the Agency
2 to derive BMDL or BMD 10 and BMDL10 estimates for
3 carbofuran is similar to the model used in the NMC
4 cumulative risk assessment and previously reviewed and
5 supported by the SAP on two occasions FIFRA SAP,
6 2005a, and b.

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

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

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

1 red blood cell acetylcholinesterase data..

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

8 **DR. HEERINGA:** Dr. MacDonald.

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

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

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

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

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

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

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

1 juvenile humans.

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

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

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

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

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

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

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

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

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

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

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

23 **DR. HEERINGA:** Dr. Bailey.

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

1 **DR. HEERINGA:** Dr. Hattis?

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

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

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

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

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

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

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

1 as indicated by the Agency.

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

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

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

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

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

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

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

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

6 **DR. HEERINGA:** Okay. Dr. Reed.

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

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

23 **DR. HEERINGA:** Dr. Edler.

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

1 **DR. HEERINGA:** Dr. Chambers.

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

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

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

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

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

25 **DR. BRIMIJOIN:** Same topic I had a

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

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

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

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

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

25 It was done in the PMD 17 study her motor

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

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

14 **DR. HEERINGA:** Dr. Lu.

15 **DR. LU:** I think the agency answered
16 that question on the data it presented. It's a PND
17 11, the age of the rat is too young to be able to
18 perform those tasks. That's my understanding so to
19 avoid to making some error in data, that's why they
20 don't, they don't do that kind of thing.

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

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

3 **DR. HEERINGA:** What I'd like to do I had
4 indicated I wanted to move to 1C but I think that maybe
5 it's time for a fifteen minute break and come back at
6 10:20 and then we will turn to question 1C. This is to
7 help people plan, it's ...I'm not going to restrict
8 discussion but if we approach the noon hour with what I
9 feel is about an hour left, I probably will go through
10 the noon hour for that.. If that doesn't appear to be
11 feasible I will call for a lunch break

12 **(WHEREUPON, a brief recess was taken.)**

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

17 **DR. ISOM:** I'm on now.

18 **DR. HEERINGA:** Thanks a lot, I
19 appreciate it. We're ready to get started here in just
20 one moment. Okay, now we're ready to resume the
21 continuation of the final morning session of our four
22 day meeting of the Science Advisory Panel. We have
23 entered into a series of charge questions related to
24 human health risks, we have had responses to questions
25 1A and 1B and we're turning now to question 1C, Dr.

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

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

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

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

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

1 carbofuran exposure in juvenile animals.

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

10 **DR. HEERINGA:** Dr. Macdonald?

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

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

1 data.

2 **DR. HEERINGA:** Dr. Bailey

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

7 **DR. HEERINGA:** Thank you Dr. Bailey.
8 Dr. Hattis?

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

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

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

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

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

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

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

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

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

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

16 **DR. HEERINGA:** Dr. Brimijoin and then
17 Dr. Edler.

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

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

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

1 was the other way around.

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

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

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

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

15 **DR. HEERINGA:** Dr. Edler

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

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

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

19 **DR. HEERINGA:** Dr. Bailey?

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

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

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

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

18 The Agency applied a 5X factor based on ratio
19 of BMD50 estimates in brain acetylcholinesterase and
20 red blood cell acetylcholinesterase in juvenile and
21 animals. Based on the currently available data does
22 the panel agree that basing its safety factor on the
23 ratio of BMD 50 estimates in brain acetylcholinesterase
24 and red blood cell acetylcholinesterase in juvenile
25 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

1 estimates of the BMD10, would narrow confidence
2 intervals.

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

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

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

1 leading us into an area where uncertainty will be
2 large.

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

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

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

1 That's an assumption.

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

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

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

1 humans.

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

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

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

1 problems as a surrogate for end cholinesterase
2 toxicity.

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

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

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

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

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

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

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

1 numerical unit there is semi log scale and plotting
2 residual AChE activity on the Y axis and taking the
3 data for the red blood cell and the brain.

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

6 **DR. BRIMIJOIN:** Right.

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

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

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

25 **DR. BRIMIJOIN:** I should also say that I

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

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

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

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

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

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

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

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

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

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

25 **DR. REED:** I agree.

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

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

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

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

1 calculation.

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

11 If you want to go back to I'm concerned that
12 the EPA when they traded those safety factor back in
13 2006 and they came up with five well I understood when
14 I got a response to my question a couple of days ago
15 was that they kind of said that that five was too much
16 back then because now it's still five and the data are
17 a whole lot better.

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

24 **DR. HEERINGA:** Dr. Chambers.

25 **DR. CHAMBERS:** I have difficulty dealing

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

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

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

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

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

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

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

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

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

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

1 that's just my interpretation.

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

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

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

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

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

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

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

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

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

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

1 **DR. HEERINGA:** Dr. Macdonald and then
2 Dr. Schlenk.

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

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

14 **DR. HEERINGA:** Thank you. Dr. Schlenk.

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

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

25 **DR. HEERINGA:** Dr. Hattis, I believe you

1 had a...

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

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

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

23 **DR. HEERINGA:** Dr. Portier.

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

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

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

14 **DR. HEERINGA:** Dr. Brimijoin?

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

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

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

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

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

25 If we make concession to the idea that the

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

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

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

20 **DR. HEERINGA:** Dr. Reaves?

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

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

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

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

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

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

3 **DR. HEERINGA:** We can return to this
4 later on.

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

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

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

16 **DR. HEERINGA:** What's the score?

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

19 **DR. HEERINGA:** Please don't score.

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

22 **DR. HEERINGA:** That would be fine, that
23 would be fine.

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

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

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

13 Shall I read it again?

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

19 **DR. REED:** Could we take that up so that
20 people..

21 **DR. HEERINGA:** Maybe if you just put it
22 in an empty color plain slide for us. While they're
23 putting up the question so that everybody is absolutely
24 clear about the question that Dr. Chambers has
25 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

1 provide reliable and robust brain

2 acetylcholinesterase data. The rationale of greater
3 sensitivity for the choice of red blood
4 acetylcholinesterase inhibition as the end point does
5 not seem reasonable from a toxicological standpoint.

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

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

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

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

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

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

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

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

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

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

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

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

12 **DR. HEERINGA:** Dr. Brimijoin.

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

24 **DR. HEERINGA:** Dr. Kehrer?

25 **SPEAKER:** Yeah, I just certainly think

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

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

14 **DR. HEERINGA:** Dr. Kehrer:

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

24 **DR. HEERINGA:** Dr. Reed?

25 **DR. REED:** As I stated before I wish we

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

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

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

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

15 **DR, HEERINGA:** Dr. Lowit:

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

14 **DR. HEERINGA:** Dr. Stinchcomb is our
15 lead discussant.

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

25 And it bases the human skin cremation of a

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

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

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

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

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

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

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

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

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

1 significantly.

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

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

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

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

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

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

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

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

1 combined with an estimate of dermal absorption.

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

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

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

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

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

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

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

1 Then the dermal applied dose can range from
2 .22 micrograms per centimeter squared per day, that's
3 based on our surface area estimates of a thousand
4 square centimeters for the hands as the smallest
5 exposure and 17000 square centimeters if the entire
6 body surface area of a 70 kilogram person is exposed.

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

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

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

1 is actually less so the percentage absorbed is higher.

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

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

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

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

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

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

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

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

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

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

4 **DR. HEERINGA:** Thank you very much Dr.
5 Stinchcomb.

6 Dr. Bunge

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

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

25 It's just extremely important that the Agency

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

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

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

25 I should say that the dermal absorption

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

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

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

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

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

4 **DR. HEERINGA:** No, I think that.

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

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

9 **DR. LU:** I have nothing to add.

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

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

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

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

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

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

10 **(WHEREUPON,** a lunch break was taken.)

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

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

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

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

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

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

25 It was also concerns expressed by several

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

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

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

25 **DR. HEERINGA:** You certainly may right

1 now.

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

4 **DR. HEERINGA:** Yes, please go right
5 ahead.

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

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

25 It goes to use patterns of this product that

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

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

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

25 They applied and put these tunnels over

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

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

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

25 **DR. MONTGOMERY:** If I could just add

1 just a little trailer on the end of that.

2 **DR. HEERINGA:** Sure.

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

11 **DR. HEERINGA:** Dr. Odenkirchen

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

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

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

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

5 **DR. HEERINGA:** Dr. Montgomery.

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

12 **DR. HEERINGA:** Dr. Grue

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

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

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

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

16 **DR. HEERINGA:** Dr. McCarty I think.

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

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

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

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

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

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

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

4 **DR. HEERINGA:** Thank you Dr. McCarty.
5 Dr. Clark.

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

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

20 **DR. HEERINGA:** Dr. DeLorme.

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

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

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

1 **DR. HEERINGA:** Dr. Sample.

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

15 **DR. HEERINGA:** Dr. Sparling and Dr.
16 Grue.

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

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

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

6 **DR. HEERINGA:** Dr. Grue.

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

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

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

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

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

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

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

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

25 It seems to me that on the human health side

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

10 **DR. HEERINGA:** Dr. Montgomery.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

19 **DR. HEERINGA:** Nu, do you want to?

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

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

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

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

22 **DR. HEERINGA:** DR. Brimijoin, I guess.

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

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

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

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

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

23 So it should require a solution that works
24 toward the default mode. So, in summary, I am
25 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

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

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

11 **DR. HEERINGA:** Dr. Macdonald.

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

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

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

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

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

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

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

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

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

9 **DR. HATTIS:** Sure.

10 **DR. HEERINGA:** Ken Portier.

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

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

25 **DR. HEERINGA:** And again, I think our

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

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

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

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

25 **DR. HEERINGA:** And I think it's the

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

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

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

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

25 **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

1 the agency is concerned.

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

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

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

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

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

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

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

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

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

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

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

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

14 Those will all be made available in the
15 public docket. I think most of those are there, on the
16 4th floor right now, and those that I have
17 electronically, I'll also try to provide. And if you
18 have anything that you have provided, especially from
19 members of the public, please make sure that I have
20 them before you leave.

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

25 To the preparations and deliberations of this

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

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

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

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

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

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

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

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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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