

US EPA ARCHIVE DOCUMENT

FIFRA SCIENTIFIC ADVISORY PANEL
OPEN MEETING

REVIEW OF WORKER EXPOSURE
ASSESSMENT METHODS

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JANUARY 11, 2007

FIFRA SCIENTIFIC ADVISORY PANEL (SAP)
REVIEW OF WORKER EXPOSURE ASSESSMENT METHODS

January 11, 2007

Morning Session

DR. HEERINGA: Good morning everyone. And welcome to the third day of our four day meeting of the FIFRA Science Advisory Panel on the topic of a Review of Worker Exposure Assessment Methods.

I am Steve Heeringa from the University of Michigan. I'm a statistician and Chair of the Science Advisory Panel, the FIFRA Science Advisory Panel for the EPA.

I'll be the Chair for today's session. And I want to thank my colleague, Ken Portier, for stepping in for me yesterday afternoon when I had a teaching commitment. Thank you very much, Ken.

At this point again as we do each morning when we open these meetings I'd like to have the members of our panel introduce themselves and state their affiliation and a little background for the audience. Ken.

DR. PORTIER: I'm Ken Portier, Director of Statistics with the American Cancer Society in Atlanta, Georgia. And my background and interest is in probabilistic issues in risk assessment.

1 DR. HANDWERGER: Good morning. I'm Stuart
2 Handwerger from the Departments of Pediatrics and Cell
3 and Cancer Biology at the College of Medicine of the
4 University of Cincinnati. My clinical area of
5 expertise is in pediatric endocrinology. My research
6 is in the developmental and molecular endocrinology.

7 DR. CHAMBERS: I'm Jan Chambers, I
8 direct the Center for Environmental Health Sciences in
9 the College of Veterinary Medicine at Mississippi State
10 University. I'm a pesticide toxicologist specializing
11 in metabolism, neurotoxicology and exposure. And I am
12 a member of the permanent SAP as well as a member of
13 the Human Studies Review Board.

14 DR. BUCHER: I'm John Bucher with the
15 National Toxicology Program at the National Institute
16 of Environmental Health Sciences. I direct the
17 Carcinogenesis Bioassay Program and the Toxicology
18 Evaluation Programs.

19 DR. HINES: My name is Cynthia Hines, I'm
20 a research industrial hygienist with the National
21 Institute for Occupational Safety and Health. I
22 conduct occupational exposure studies, including a
23 number in pesticides.

24 DR. JOHNSON: My name is Dallas Johnson.
25 I'm a retired professor of statistics from Kansas State

1 University. I've spent more than 30 years consulting
2 on agricultural type problems.

3 DR. APPLETON: I'm Hank Appleton with the
4 Forest Service of the U.S. I'm a pesticide
5 toxicologist and risk assessor and I've accumulated
6 about 20-odd years of experience in conducting exposure
7 assessments for pesticides.

8 DR. KIM: I'm David Kim, I'm from the
9 Department of Environmental Health at Harvard School of
10 Public Health and my research area is in human exposure
11 assessment and pharmacokinetics.

12 DR. BARR: I'm Dana Barr, I'm from the
13 Centers for Disease Control and Prevention in Atlanta,
14 George. I'm the Chief of the Pesticide Laboratory. My
15 primary research focus is in assessing human exposure
16 to environmental toxicants with a specialty in
17 pesticides using biomonitoring.

18 DR. LU: Good morning. I'm Alex Lu from
19 the Rollins School of Public Health at Emory
20 University. My research interest is using biomarkers
21 to assess pesticide exposures and using the
22 pharmacokinetic model to interpret those biomarker
23 data.

24 DR. HUGHES: My name is Brian Hughes, I'm
25 a toxicologist. I'm with the Pesticide Section of the

1 Michigan Department of Agriculture. My interest is in
2 risk assessment and also in doing studies for, field
3 studies for occupational risks in conjunction with
4 Michigan State University.

5 DR. LANDERS: My name is Andrew Landers.
6 I'm an agricultural engineer at Cornell University. My
7 role there is to head the Application Technology Group
8 where we look at the engineering ways of reducing
9 operator contamination and the environmental pollution.
10 My research is looking at ways of improving deposition
11 and reducing drift.

12 DR. MACDONALD: And my name is Peter
13 MacDonald. I am Professor of Mathematics and
14 Statistics at McMaster University in Canada. My
15 general expertise is in applied statistics and this is
16 my seventh year on FIFRA panels.

17 DR. HAMEY: Good morning, I'm Paul Hamey.
18 I'm from the U.K. government's Pesticide Safety
19 Directorate where I'm responsible for Human Exposure
20 Assessments.

21 DR. ROBSON: Good morning, I'm Mark
22 Robson. I'm the Director of the New Jersey
23 Agricultural Experiment Station and Professor of
24 Entomology at Rutgers University and Professor of
25 Environmental Health at our School of Public Health.

1 My primary responsibility is administrative, but when I
2 did honest work I did work looking at farmer and farm
3 worker exposure to pesticides.

4 DR. POPENDORF: And I'm Will Popendorf,
5 Professor of Industrial Hygiene at Utah State
6 University. I focus on exposure assessment and control
7 of chemical hazards and I've got 30 years experience in
8 agricultural exposures to chemicals.

9 DR. CURWIN: Good morning, I'm Brian
10 Curwin with the National Institute for Occupational
11 Safety and Health. My primary research interest is
12 occupational exposure assessment with a particular
13 interest in pesticide exposure.

14 DR. HEERINGA: Thank you very much members
15 of the panel. I'd also like to introduce the
16 Designated Federal Official for today's meeting, Myrta
17 Christian. Myrta tells me she has no information to
18 give us this morning so just with the introduction I
19 think we're ready to move on.

20 As we do each morning we're going to open
21 with a session which gives presenters an opportunity to
22 provide short follow ups on discussions from the
23 previous days to clarify points or provide some
24 additional information that may have been requested or
25 a need arose during the discussion.

1 I'd like to turn to Jeff Dawson and Jeff and
2 Evans to see if there are some initial follow ups from
3 the EPA team at this point.

4 MR. DAWSON: I just had one followup
5 thought from yesterday about, and there was some
6 discussion about this issue yesterday about why a kind
7 of broadly generalizable generic database for exposures
8 is very important for us as a program.

9 I just put together a couple slides to kind
10 of illustrate, you know, where we are as a program and
11 the level of effort we have around conducting
12 occupational exposure assessments.

13 So just to give everybody some perspective,
14 over the last 10 years basically under the re-
15 registration program in EPA we essentially conducted
16 occupational exposure assessments related to the
17 reevaluation of about 10,000 food tolerances, so quite
18 a lot of work as you can probably understand. And that
19 involved looking at basically hundreds of active
20 ingredients, I don't have an exact count, I apologize
21 for that. But, you know, it's 300 to 400 or so active
22 ingredients over that time frame.

23 And also in the registration program with new
24 chemistries coming online we've looked at over 100
25 cases or so also over that 10 year period. And the one

1 thing to point out related to the new chemistry cases
2 is that, and I think somebody brought this up
3 yesterday, is that, you know, we don't have monitoring
4 data for those specifically so it becomes very
5 important because we're very limited as to how we can
6 evaluate those prior to them, you know, being released
7 into the marketplace.

8 And then the antimicrobial folks also have,
9 you know, hundreds of active ingredients that they're
10 going through and doing reevaluations on at this point.
11 So that, to put it in context.

12 And I had one more slide as well, so John
13 Worgan on Monday had talked about, or Tuesday, sorry,
14 had talked about the tiered approach. So basically on
15 our tiered approach, tier 1 is the lowest amount of
16 resources and data needs and complexity and chemical
17 specificity related to the exposure data so we use
18 that.

19 This is a kind of tool for that. And also
20 for tier 2 we begin to increase the amounts of data.
21 We may have a specific monitoring study or something
22 that goes with that chemical or more information about
23 use patterns and such that we try to incorporate. But
24 we don't move up the tiered process unless we need to.
25 If something passes our tier 1 approach with flying

1 colors we're not going to invest any more resources in
2 it. And then as we move up to tier 3 that tends to be
3 just out of whatever context where we tend to see the
4 investment on the registrant's part and others and
5 doing more complex kind of analyses where you get more
6 chemical specific data.

7 It may be more passive dosimetry monitoring
8 studies, it could involved biomonitoring and even we've
9 done, you know, a few cases over the last couple years
10 where we've done kind of highly complex multi
11 compartment pharmacokinetics modeling to look at dose
12 levels in the tissue, those kind of things. So our
13 target organs. But they become highly complex cases
14 and there's a lot of resource investment and we tend to
15 only get to that point if we need to.

16 As far as validation tools, I mean we
17 certainly want to bring all the tools available to use
18 related to, you know, validation and evaluation of the
19 methodologies as well. So I'm not saying that we
20 wouldn't use, on a routine basis we would use, try to
21 use the generic approach as much as possible but as far
22 as the analysis and validation steps we want to bring
23 everything to the table. Thanks.

24 DR. HEERINGA: Jeff.

25 MR. EVANS: Yes, thank you. I'm Jeff

1 Evans with the Health Effects Division. And I just
2 want to clarify a point that I believe is on page 61 of
3 the background document where we talk about how to
4 resolve the issues of hand rinse performance and other
5 breakthrough issues with the passive dosimetry.

6 And what we were thinking about in addition
7 to perhaps correcting based on physical chemical
8 properties but also perhaps incorporating into the
9 study design a biological monitoring component, not
10 necessarily to compare with the passive dosimetry
11 measurements were, but in fact to confirm if there was
12 breakthrough.

13 So if there was anything that was not
14 recovered from the face wipes or the hand rinses it
15 perhaps would show up in the urine and that would be a
16 way just to kind of confirm those issues of
17 breakthrough and inefficiencies in hand rinse
18 performance. So I just wanted to make that clear.
19 Thank you.

20 DR. HEERINGA: Thank you very much. At
21 this point too in terms of additional followup there is
22 I've asked Doctor Ross, representing the AG. Handlers
23 Task Force to come forward. They have a few additional
24 followup pieces of information that they as a task
25 force would like to provide to the panel too. So

1 Doctor Ross.

2 DR. ROSS: Thank you, Mr. Chairman,
3 members of the panel. As you recall there were
4 questions about the data that was excluded from the
5 comparison of passive dosimetry and biomonitoring
6 yesterday in my presentation and I referenced Table 7
7 which is shown on this slide, at least half of it.

8 The reasons for excluding these various
9 studies basically fall into three categories. One is
10 the lack of primate dermal absorption and/or
11 pharmacokinetics. Another is the biomonitoring being
12 less than or equal to the limit of quantification at
13 many of the intervals at which samples were collected.
14 And finally one of the significant issues was studies
15 in which significant body parts that we would expect to
16 have high levels of exposure were either not
17 represented or sporadically represented in the data.

18 For example if you look at the right hand
19 column of the first row on Cowel 1987, there was no
20 hand monitoring done in the studies of
21 mixer/loader/applicators. Now we know from other
22 studies of this nature that hands can contribute up to
23 50% of the dosage. So if the hand was not monitored
24 and in addition the legs, the lower legs were not
25 monitored and there was no inhalation monitoring in the

1 study so it has significant shortcomings, defaults.

2 In the case of the next study, also by Cowel,
3 there was extremely low primate dermal absorption, and
4 by extremely low I mean .08 percentage of an applied
5 dosage was absorbed. And as Doctor Popendorf indicated
6 yesterday, the error associated with extrapolation from
7 that kind of low dermal absorption is going to be
8 phenomenal. So we didn't feel that it would be
9 appropriate to include that data set within the data
10 that we did the comparison of the passive dosimetry and
11 biomonitoring.

12 Next study, Fenske, 1988, there was
13 incomplete data reporting and by incomplete I mean that
14 there were data provided for body regions in terms of
15 micrograms per centimeter squared, but the body regions
16 were not representative of an entire body.

17 In other studies like Bernard, 2001, Krager,
18 1996, the post-exposure biomonitoring data was
19 extremely low. In the case of the Krager study with
20 Borax, we know that the human dermal absorption is
21 0.2%. We wouldn't anticipate that there would be very
22 much coming out in the urine and in fact, despite high
23 dermal loadings there was not any above background.

24 For the two Rotunaro studies on vinclosylin
25 there is no primate dermal absorption of

1 pharmacokinetics/metabolism, so we don't have anything
2 with which to reference back to the human study. There
3 might be rat data but as I had indicated before, that
4 can be very deceptive in terms of trying to emulate
5 human kinetics or metabolism.

6 The case of the Dubelman, 1989 study, again
7 there was a mixer/loader/applicator study with no hand
8 monitoring.

9 And the last on this page, Levy, there were
10 samples not present, they had been mentioned in the
11 document as being lost. There were no hand residues,
12 no lower arm, lower leg samples of any kind and again,
13 these are significant in terms of the work activity
14 that these people were conducting. So you wouldn't
15 expect to be able to get any kind of meaningful
16 assessment out of this kind of data. You can get a
17 qualitative idea but not a quantitative idea.

18 And I don't know, want to bore you with going
19 through the rest of these but the story is similar.

20 At this time I'd like to turn over the
21 comments to Curt Lunchick.

22 DR. HEERINGA: Yeah, Mr. Lunchick. Thank
23 you, Doctor Ross.

24 MR. LUNCHICK: Thank you panel. We just
25 wanted to make a clarification in regards to the

1 comparisons that have been raised between the number of
2 observations in the Pesticide Handler Exposure Database
3 compared to what is the anticipated or possible within
4 the AG. Handler Exposure Database.

5 Specifically for example, Doctor Fenske in
6 his written comments compared the 1,700 monitoring
7 events in PHED to approximately 600 that would be in
8 the AG. Handler Exposure Database. And I think we need
9 to look at the quality of the data to make a more
10 direct comparison and I think this may be important as
11 we get into discussions on sampling sizes later in this
12 panel meeting.

13 I actually have a working copy of the
14 database and went into the Pesticide Handler Exposure
15 Database applicator file to use as an example. And
16 there are a total of 715 records in the applicator file
17 which range from aerial and ground boom type of
18 applications all the way down to nonagricultural events
19 such as hose and sprays and aerosol cans. If you look
20 at long sleeved shirt, long pants and no gloves, of
21 those total of 715 records your number of observations
22 ranged from 350 on the thighs up to 564 on the hands.
23 Now that's all data grades.

24 The Agency prefers grades A and B data and
25 that's typically what the registrants use when they try

1 to do their assessments too. If you subset this to
2 dermal grade A and B which is just the dermal
3 dosimeter, it's not the hands, you're reduced now to
4 358 records and a total of 214 to 293 data observations
5 on different parts.

6 Now, if you look at the hands, and these are
7 totally independent of the dermal areas, grade A and B,
8 there are 365 records, of which 259 provide data
9 without gloves. If you wanted to get down to those
10 records that were grade A and B for both dermal and
11 hands at the same time, you're actually now down to 248
12 records of which you now have a total of 133
13 observations to 215 observations of data.

14 Now as it was mentioned also our selection
15 criteria was to make sure we had some type of dosimetry
16 on all parts of the body. The Pesticide Handler
17 Exposure Database in its statistical function allows
18 you to select for what is called complete data sets and
19 you can define that.

20 Defining the complete data set as having head
21 exposure, hand exposure and exposure to the 10 parts of
22 the body that are part of the AHETF criteria which is
23 essentially upper arms, lower arms, chest, back, the
24 thighs and lower legs, you're now reduced to a total of
25 57 records of which the use patterns will range from

1 agricultural to nonagricultural and to put it in
2 perspective as we talk about proportionality today, out
3 of those 57 only 27 records provided data on the
4 application rate in pounds AI per acre. So there's a
5 very big difference between the total number of data
6 points in the database to those that are comparable to
7 the quality of data that we are looking for in the
8 AHETF program.

9 DR. HEERINGA: Thank you very much, Mr.
10 Lunchick. At this point I believe that we also have a
11 followup comment from Doctor Doug Baugher.

12 DR. BAUGHER: Yes, thank you. Yesterday I
13 jokingly voted New York off the island when I learned
14 that they operated at the high end of the label. On
15 reflection I realize that I wrote the model to create
16 the perfect storm, that is the co-occurrence of the
17 high rates of application, the high acreage, the low
18 residue recovery efficiencies and everything else. And
19 therefore the New York scenarios would be included in
20 the upper percentiles where we normally look for safety
21 assessments. So welcome back.

22 Secondly, yesterday afternoon there was a
23 comment and a concern which was well founded, that with
24 the handler studies where gloves are worn, exposure of
25 the hands may be fairly low but during reentry they may

1 be fairly high and the residue inefficiencies of hand
2 washes could be important for reentry. I mentioned
3 that I had done a second run with a high exposure
4 reentry scenario and I'll give you a couple pieces of
5 information.

6 For the air blast applicator wearing gloves,
7 20% of the exposure was to the hands. For orchard
8 harvesters and thinners, 70% of exposure was to the
9 hands. Counter-intuitively the impact of handwash
10 inefficiency was less in the reentry model than in the
11 handler model. And the reason is pretty
12 straightforward. The reentry model has more parameters
13 with characterized distributions and they just tend to
14 swamp out the uncertainties associated with residue
15 recovery inefficiencies. So the conclusions were the
16 same for reentry as for handler, but even stronger.

17 DR. HEERINGA: Thank you very much, Doctor
18 Baugher. Based on this additional information, any
19 questions of clarification from the panel members?
20 Okay, well let's move on then to the morning's
21 proceedings and I think that at this point in time we'd
22 like to welcome Matthew Crowley and David Miller of the
23 Health Effects Division who have a presentation on the
24 proportionality assumption between exposure and the
25 amount of active ingredient handled, critical

1 assumption in the total exposure assessment.

2 MR. CROWLEY: Good morning everybody, I'm
3 Matthew Crowley in EPA's Health Effects Division. I
4 knocked over some stuff over here, sorry for the
5 confusion.

6 Along with me I have David Miller, also in
7 the Health Effects Division and I'd like to thank him
8 for his help in doing the statistical analysis on this
9 presentation along with members of his staff.

10 So this morning we will be going through the
11 assumption of proportionality between exposure and the
12 amount of active ingredient handled, and that is the
13 unit exposure that has been mentioned frequently in the
14 past couple of days.

15 First I'll go through some introductory
16 materials, the purpose and background and a brief intro
17 into the case studies. Then I'll follow with data
18 manipulation formatting, the actual analysis and then
19 some discussion points.

20 So the overall purpose is to discuss the
21 assumed proportional relationship between exposure and
22 the amount of active ingredient handled, for brevity
23 noted as AAIH in this presentation and likely in the
24 task force presentation to follow this afternoon. So
25 that is an example of format there, the x milligrams

1 exposure per pounds handled that we use in our risk
2 exposure and risk assessment calculations. And that's
3 just an example. Canada may use micrograms per
4 kilogram pounds handled. And we'll be using the 6 PHED
5 case study scenarios that Jeff Dawson went through
6 earlier this week and following that as this follows
7 with the charge to the question and asked to comment on
8 this relationship in light of the historical precedent,
9 its application in risk assessment and subsequent risk
10 management decisions, the analysis shown here and in
11 the background document and the study design objectives
12 of the AG. Handler Task Force.

13 Briefly I've presented here a plot from
14 Reiner and Sevard in 1985 and this is also taken from
15 our Subdivision U Guidelines presented to the SAP in
16 1986. This graph is for air blast applications, each
17 point is a mean of a number of exposures, that's why
18 the value there is 23 but they're all the mean. And
19 the authors noted that the r value of 0.7 in the
20 Spearman Rank correlation was remarkable considering
21 the umbrella of uncertainty involved.

22 On the x axis you have the application rate,
23 pounds AI per acre, and dermal exposure in milligrams
24 per hour. And then the core at the bottom is one of
25 the few that I saw directly relate to the amount

1 handled or applied as opposed to the application rate
2 or the exposure in milligrams per hour.

3 So again the 6 case study scenarios, I don't
4 think I need to rehash anything, I think Jeff Dawson
5 did a good job of explaining. If anybody has any
6 thoughts or clarification on what is any of these
7 equipment or formulations we can certainly talk about
8 that.

9 The next set of slides will be a discussion
10 of how we use the PHED data, how we put it into the, a
11 reasonable format to channel Doctor Johnson's published
12 works it's going to get messy in here.

13 So again most of the problems and issues
14 related with the PHED data, at least for this analysis
15 was the composite worker methodology, it has other
16 synonyms as well. And again as a reminder this is how
17 the unit exposures are calculated on a body part by
18 body part basis across individuals and you know if you
19 went through the lognorm, you know, the geometric mean
20 and the mean for the distribution that was determined
21 for that set of body parts. So the specific issues
22 I'll be talking about are the grading criteria, again
23 briefly and then the concurrence of measurements across
24 body sections and then patches and whole body
25 dosimetry.

1 The concurrence of measurements across body
2 sections, actually Curt kind of just, Curt Lunchick
3 kind of just touched on that as well in the discussion
4 of the workers that actually had gloves on at the same
5 time as normal work clothing and that sort of stuff.

6 So again the PHED grading criteria and our
7 surrogate table, the grading based on laboratory and
8 field recovery and as has been discussed, most of our
9 assessments attempt to use A and B grade data only.
10 And for this analysis we could have simply used the
11 entire A through E data, however we split it up into
12 various combinations and these combinations were not,
13 you know, meant to recommend for a risk assessment of
14 anything of that sort, it was just meant to optimize
15 the data and show a number of plots.

16 Problem 2, again I mentioned the lack of
17 current measurements of body sections and the lack of
18 concurrent inner and outer dosimetry measurements. For
19 example, and what I mean by inner and outer dosimetry
20 measurements is gloved hands and normal work clothing,
21 in some instances that was not the case. There we'd
22 have, measure their bare hands with normal work
23 clothing on and in that case it was difficult to
24 combine the two to present a measurement of total
25 dermal exposure.

1 So our solutions to this were just to use the
2 data as it was presented, as we had it and this was by
3 analyzing hands separately, just the body, you know,
4 the torso, arms and legs, chest and back and then total
5 dermal when the measurements were concurrent, either
6 completely outer dosimetry, bare hands and then
7 deposition of residue on the body or total dermal
8 underneath a single layer of clothing, normal work
9 clothing and gloves for the hands. And also analyzing
10 both inner and outer dosimetry.

11 For this analysis though we may use these,
12 the combination in risk assessment, we did not present
13 the combination of outer, for example, outer head plus
14 inner body for air blast applications. In that case we
15 have just presented the head for the purposes of just,
16 of showing that and the inner dosimetry may be trumped
17 by the outer head patch. And also for inner dosimetry
18 we recognize that the uncertainty that has been
19 discussed previously, the inner, the penetration
20 underneath, you know, the protective clothing or the
21 normal work clothing and the treatment of non-detects,
22 one half the limited detection or quantification.

23 It should be noted that these hands and body
24 and head and inner and outer dosimetry, these
25 separations are, do have some practicalities in terms

1 of applying protective equipment and that sort, so it
2 does relate in a sense to risk assessment and PPE
3 practicalities. However it also was beneficial for the
4 analysis just to present proportionality across body
5 sections.

6 And the third problem being the biggest
7 problem of using the data as a whole, the whole, an
8 attempt to use the whole database and now the problem
9 is combining patches and whole body dosimetry. As we
10 know, in patch dosimetry not all body parts were
11 necessarily measured. Now this is okay for PHED
12 analysis because of the composite work or methodology
13 discussed. And with whole body dosimetry, whether it
14 was a true whole body dosimeter like a union suit or a
15 top and bottom, all the body parts were measured and
16 by, you know, body I'm talking about again the torso
17 and the arms and legs.

18 And the whole body dosimetry measurements
19 couldn't be separated to match with any of the patches
20 that, you know, we would just choose for the analysis
21 because in the software the whole body dosimetry was
22 basically broken up into body parts and an equal value
23 given to that body part and then adjusted for the
24 surface area of that body part. It was, they were
25 added later than the patch dosimetry data so it was

1 needed to do that to, for the amenability with the
2 software.

3 And you may have noticed this going through
4 any of the raw data that we provided that you saw equal
5 measurements for, you know, the forearm and lower leg
6 and that was in most cases because of the whole body
7 dosimetry. So our solution was to use a minimum of
8 critical body parts for the patch data.

9 And across all scenarios these were, we chose
10 the forearm, chest, back and thighs and according to
11 the surface areas in the PHED reference manual this
12 represented approximately 60% of the total body. And
13 we thought this was a reasonable combination of the
14 data from the patches with the whole body dosimetry.
15 And again that is only talking about the torso, those
16 body parts would then be added to the head or the
17 hands, depending on the scenario

18 So here is just an example, this is open cab
19 air blast applications, outer dosimetry only. And the
20 table on the left shows what was available in PHED and
21 the table on the right shows what was used in the
22 analysis, the yellow being, the yellow highlight being
23 what was used and minimum again being the forearms,
24 chest, back and thighs.

25 And you can see we went, as Curt Lunchick

1 mentioned this morning you go from 77 total monitoring
2 events to 56 that had at least the minimum.

3 So now we're getting into the analysis
4 starting with some statistical background and
5 mathematical background and then getting into the
6 actual plots.

7 The method used is a log log linear
8 regression and the directly proportionate relationship
9 between two variables, x and y exists if a plot of $\log$
10 x versus $\log y$ produces a straight line with a slope
11 of 1.

12 This is an involved slide but I will try to
13 go through it fairly quickly. The first box there, the
14 objective is to evaluate whether a proportionate
15 relationship exists and for example if you double the
16 amount of active ingredient handled we assume that the
17 exposure is then doubled. And the first box is the,
18 basically the unit exposure reorganized into the
19 mathematical equation shown.

20 And throughout, you know, with showing the
21 log on both sides throughout we are focused
22 specifically here on the coefficient B_1 and the
23 equation after you log both sides of the original 1,
24 the B_1 is then the slope of the line that, and we are
25 looking for the slope of the line to be 1 or not

1 significantly different than 1. Using a 95% confidence
2 interval of the slope as a significance test and the
3 plots that you will see are ordinarily square
4 regressions, however we do have, since the background
5 document, conducted some hierarchical linear modeling
6 and that will be discussed as well.

7 So the next set of plots that you're going to
8 see have all these various characteristics that are
9 shown up here, the PHED grading will be noted in the
10 title of the plots, whether it's inner or outer
11 dosimetry, the statistical information will be noted on
12 there, all of them I believe are in the upper left hand
13 quadrant. And we'll be discussing some of those
14 statistical limitations as we go through them.

15 Also I will be going through some anecdotal
16 data characteristics and I will be just discussing non-
17 detects and inter and intra-individual variability and,
18 you know, some other factors. And I think this is
19 important because it gives another view of the data
20 and, you know, we'll be discussing proportionality but
21 there is value added to some of the anecdotal stuff
22 that I'll be, anecdotal factors I'll be talking about.

23 And from exhibit C there were 35 plots shown,
24 we're only, I'm only presenting 4 here. I have loaded
25 onto the laptop here all 35 in slide form in case

1 anybody is particularly interested in any one of them.
2 We can bring them up. Unfortunately I probably won't
3 be able to talk as much at length about those as I will
4 the current ones because there's a whole lot of data.

5 So the first one shown here is the open cab
6 air blast applications and this shown is only the head
7 exposure and that is the outer dosimetry. PHED grades
8 A through D and you notice on all these plots the
9 exposure is on the y axis in micrograms and the pounds
10 of active ingredient handled is on the x axis. They
11 are both log scale, the solid black line is the
12 regression line.

13 The dash black line is a slope of 1 line.
14 For comparison the blue dash lines are the 95%
15 confidence interval. And each data point is color and
16 character coded and again they represent, each point
17 represents a single monitoring event. In this case
18 again they are the head only. And we chose this one to
19 show first, I was told to put my best foot forward, and
20 at the beginning we had, we were on, we assumed that if
21 we were going to see anything because of the
22 uncertainties with inner dosimetry, that outer
23 dosimetry would likely probably show the best
24 relationship. So, and in this one it appears that, you
25 know, this is a reasonable situation.

1 Here's study 435, there were 4 workers, each
2 conducting the activity twice, again open cab air blast
3 applications. And this is the breakdown of the workers
4 showing some of them close together, some of them not
5 very close together and this again may get into the
6 inter and intra-worker varia individual variability
7 that we'll discuss later.

8 This is the same worker, he has conducted on
9 consecutive days, one in the afternoon and one in the
10 morning and, you know, we're seeing almost a threefold
11 difference with the same person. This is the only D
12 grade data, data point on this plot without this point
13 as you'd see I believe I included it in exhibit C, the
14 A through C, head only exposure for this scenario and
15 the slope of that line is 0.79.

16 Study 1006, it's one worker conducting the
17 activity 5 times, all 1 hour applications on the same
18 day. And the, it just so happens the one in the
19 morning for an hour was approximately 5 times greater
20 than the one in the afternoon for an hour. And the
21 only non-detect on this plot is this worker from the
22 study 442. It might be worth it to note that this
23 limit of detection was quite a bit higher than the
24 white squares and red squares right next to it. That
25 gets into, you know, again the uncertainty.

1 We've also provided the conversion of that
2 regression line onto the original scale. On the
3 original scale we would assume that there would be no
4 exponent there, that would be an exponent of 1. And so
5 it's just there for comparison. And again that almost
6 looks like a straight line but it actually will plateau
7 with a slope less than 1, with an exponent less than 1.

8 The next plot is open mixing/loading liquids.
9 This is a bare hand exposure, only grades A and B.
10 This slope rejects, this plot rejects independence but
11 proportionality may not be reasonable in this case, a
12 slope of 0.16.

13 In study 434, this is the same worker in
14 Pennsylvania. The collection method was cotton gloves
15 and the difference basically in his exposure was
16 between the morning and the afternoon. And his left
17 hand, the left hand in the morning was a much higher
18 exposure than the left hand in the afternoon.

19 Study 9003, two workers conducting the open
20 mixing/loading twice at about 0.3 pounds handled and
21 it's, and these are also cotton gloves. And in this
22 case you might think that both of those, that's
23 actually 4 points, both of those at the top might be
24 the same worker and both of those at the bottom might
25 be the same worker, but it's not, it's the reverse.

1 In this case, study 9001, three workers, each
2 doing it three times. This is perhaps the opposite
3 situation of what I've just showed because worker C had
4 the three lowest while worker A and B were pretty much
5 at the top.

6 In study 465 the 6 workers each conducting
7 the operation once and again they're all, so far all
8 are shown in the collection method of cotton gloves.
9 And as might be expected, although maybe the minutes
10 aren't that significantly different but I thought it
11 would be worth it to point out the longest in that
12 entire study was 20 minutes and that was the highest
13 exposure as might be expected, but the second highest
14 was the shortest time period of open mixing/loading the
15 liquid.

16 In study 9010 they used a rinse methodology
17 to collect these on 2 workers each conducting it 5
18 times, the operation 5 times. And worker A has
19 consistently the highest for those measurements but
20 also has the lowest.

21 In study 447 again 2 workers, each 3 times
22 collected with the rinse methodology so it shows here
23 that we are comparing as if they are equal. The both
24 collection methodologies. And again the conversion
25 onto the original scale.

1 The next plot I'm showing is open loading
2 granules. This is actually total exposure underneath
3 the normal work clothing and the hands are underneath
4 gloves. This is one of the few, I believe it was 4 of
5 the 35 that actually wound up with a slope greater than
6 1. Most of the others had a slope less than 1. And
7 there are only studies in this case from about 7 to I
8 think to 66 pounds handled.

9 Study 1004, 6 workers, each doing it a couple
10 of times to get to 15 measurements total, these are all
11 A grade. These values here are all non-detects and
12 these values here are, the body value is all non-
13 detects so it brings into the uncertainty of the
14 treatment of those. Again anecdotally these are both,
15 there are 2 data points there, 2 different people. In
16 one person the majority of the exposure came from their
17 body. The other person, the majority of the exposure
18 came from their hand, hands, sorry.

19 In study 1011 there are no non-detects in
20 this having multiple workers performing the operation
21 multiple times to get 27 measurements, A and B grade.
22 There is what the, on the original scale what a slope
23 greater than 1 would look like. In this case a slope
24 of 2.21.

25 The last plot I'll be showing is, well you

1 know, probably the ugliest one that we've seen. Open
2 loading granules, this is bare hand exposure again,
3 however all these data points here are grades D and E,
4 a slope of, I believe the only slope less than, you
5 know, a negative slope.

6 In study 425 here using cotton gloves again
7 to collect the residue, all D grade, there's 3
8 different workers. The operation lasted between 3 and
9 5 minutes.

10 With study 448 the operation lasted between
11 2.5 and 4 hours, at least I believe the operation may
12 have lasted 2.5 to 4 hours. The open loading, the
13 loading of the granules may have been like the previous
14 study, only a couple of minutes and they did not
15 collect the residue until half the day and they had
16 done other activities. So these are all E grade.

17 DR. LU: This is Alex Lu. Just a
18 clarification. You just mentioned those are for bare
19 hands. But the subjects before had gloves.

20 MR. CROWLEY: The gloves means the residue
21 was collected with cotton gloves as opposed to a hand
22 rinse collection.

23 DR. LU: And how about the previous case,
24 the inner dosimetry, the previous slide, yes. How
25 about those, their hands? How did you sample their

1 hands?

2 MR. CROWLEY: I do not know. I can,
3 that's within the database but I'm not sure. It was
4 difficult to know every specific about everything.

5 DR. LU: Okay, thank you.

6 MR. CROWLEY: You're welcome. So this is
7 the case in 448 where there was only, this is the only
8 case where a worker performed the same, the task twice
9 and he was measured twice.

10 And again this is a note again about the time
11 to residue collection. Basically the same residue, the
12 difference being 22.5 pounds handled versus 750 pounds
13 handled and then 3 minutes versus 2.5 hours. I'm just
14 not sure from the data whether that was a 2.5 hour
15 operation of they just collected the residue following
16 the morning's operation. And again the original scale
17 inset.

18 So some of the limitations that were
19 discussed following the initial exploratory analyses
20 using ordinary least squares, you saw from, in various
21 cases the clustering of the studies and ordinarily
22 these squares treat each data point independently so
23 that violates the ordinary, that ordinary least square
24 assumption. And the study design may implicate a more
25 appropriate nested or hierarchical linear modeling

1 method because of the measurements within workers
2 within studies problem that we have.

3 In this table, sorry it's not very well read,
4 however it compares the ordinary least squares against
5 the results that we have gotten to with hierarchical
6 linear modeling, the difference in the regression
7 slope and the 95% confidence limits. The highlighted
8 ones in red are those that, where before a slope of 1
9 was not included in the confidence limit, that using
10 the hierarchical linear modeling method, it now does.
11 And I've shown the corresponding slides of the previous
12 4 plots. Those other 4 had been ones I was going to
13 show as well so we performed the hierarchical linear
14 modeling on those but I can bring those up. As I said
15 I have those, the slides on the computer:

16 Now again to some discussion points. Again,
17 as has been discussed throughout the past three days,
18 there is data limitations with PHED, the combination of
19 patches, the small range of magnitude, amount active
20 ingredient handled, clothing penetration factors,
21 treatment of non-detects and then the rise methodology
22 and as a result, can we draw reasonable conclusions
23 using the PHED data for the relationship between
24 exposure and the amount of active ingredient handled?
25 And we note that an improved study design could resolve

1 these issues or, you know, completely control the
2 experimental design where you could, where you would
3 control everything and you could determine the
4 relationship better. But that likely is not the case
5 for us.

6 Additional points I wanted to bring up is
7 how, you know, in light of how this has historically
8 been used in risk assessment and its practicalities for
9 risk management decisions, we can limit in various ways
10 the amount that a person can handle so it fits well in
11 our risk assessments.

12 But we also propose there could be
13 alternative predictors of exposure, exposure duration,
14 alternative metrics for application rates in
15 concentration, however, with the last two there might
16 be some, correlating with the pounds of, amount of
17 active ingredient handled.

18 But this, I believe that decoupling in a
19 closed loading system was brought up previously during
20 this week and that could be a situation that we would,
21 you know, maybe look into where the exposure is better
22 predicted by the amount of times that they lock and
23 load the closed system as opposed to the amount that is
24 actually going through the system.

25 The next point about conservatism of assuming

1 proportionality, as I've shown, only 4 of the 35 plots
2 had regression slopes greater than 1 which would not be
3 conservative. However I think for, I'm not sure, two
4 of those, half of those, it had a slope greater than 1
5 but the confidence limit also included a slope of 1.
6 But there are a couple where it did not include 1 and
7 the slope was greater than 1. So it appears in most
8 cases that the high end will be conservative however
9 that doesn't, we may be underestimating at the lower
10 amount handled.

11 And we've also discussed are our current
12 scenarios appropriate? Can certain scenarios be
13 combined or conversely do certain scenarios need to be
14 subsetting? For example is there a significant
15 difference between granules and dry flowables? Or
16 should there be a separate unit exposure for high
17 amounts of active ingredient handled versus low amounts
18 of active ingredient handled? And the first example
19 again would get into the problem of how this all fits
20 into risk management, regulating a dry flowable
21 formulation using granule data and how that would work
22 out.

23 So finally perhaps the understatement of the
24 week, the current data is not designed specifically to
25 address this issue however we feel that with the

1 improved study design we may be able to do more
2 advanced statistical analysis and it will aid in either
3 reinforcing this assumption or perhaps informing the
4 applicability of another predictor of exposure. And
5 that is all I have. Thank you.

6 DR. HEERINGA: Thank you very much,
7 Matthew.

8 MR. CROWLEY: You're welcome.

9 DR. HEERINGA: Questions from the panel on
10 data presented. I know Alex had a question before. Do
11 you have any follow ups at this point?

12 DR. LU: No, I don't.

13 DR. HEERINGA: Doctor Popendorf and then
14 Doctor Bucher.

15 DR. POPENDORF: That was an interesting
16 presentation and a good explanation. But I just
17 wondered, some very similar plots were in the review
18 document and I wondered if you could just discuss how
19 those that we had earlier differed from what you're
20 presenting today?

21 MR. CROWLEY: The results were all over
22 the place. In some instances I could have shown all
23 plots that had, all slopes of 1 with tight confidence
24 intervals but I chose to show one. In other cases,
25 there was only one that I showed that had a negative

1 slope. Hold on one second

2 DR. POPENDORF: Well then maybe a simple
3 explanation to clarify, that that we were presented in
4 the review is part of what you did, but didn't show, is
5 that true?

6 MR. CROWLEY: Yes.

7 DR. POPENDORF: Okay, so

8 MR. CROWLEY: There were, there were many
9 more, the methodology was basically the same for
10 everything else but again there were 35 of them and I
11 just

12 DR. POPENDORF: Yeah.

13 MR. CROWLEY: there were really, I
14 think I could have picked any to show and the same
15 anecdotal characteristics would have come out for each
16 one.

17 DR. POPENDORF: Okay.

18 MR. CROWLEY: But, you know, it was kind
19 of a good, bad and ugly show.

20 DR. POPENDORF: Okay, and the ROB, rest of
21 body in here are the same critical

22 MR. CROWLEY: Yes.

23 DR. POPENDORF: body parts? Thanks.

24 DR. HEERINGA: Doctor Bucher and then
25 Cynthia Hines.

1 DR. BUCHER: Again from a naive standpoint
2 I was just wondering if the Agency has any explanation
3 for any reality associated with a proportion greater
4 than 1? More active ingredient exposure in relation to
5 the pounds of pesticide used. Is there any situation
6 under which one would realistically envision that
7 occurring?

8 MR. CROWLEY: I cannot think of anything
9 off the top of my head. David?

10 MR. MILLER: Yeah, we had talked about
11 that, we can potentially understand a proportionality
12 of essentially less than 1 simply because we talked
13 about, a little bit about the caking affect as you get
14 a certain amount on there. But just it going up, I
15 mean it's almost like the person would be a magnet for
16 it. The more they handle the more it gets attracted to
17 them which just seems strange to us.

18 DR. HEERINGA: Or the more they handle the
19 sloppier they get. Doctor Popendorf.

20 DR. POPENDORF: I was looking at that
21 earlier data that we had available and was going to
22 make this comment later, but one explanation if you
23 look at a lot fo the examples in the review at least
24 where the slope was greater than 1, was the inner data
25 and the outer data was 1 or less. And one explanation

1 would be the inner data, if you're building up dose on
2 the clothing, it takes awhile to penetrate, if you
3 assume a constant rate over time the people that handle
4 more are going to have longer exposures and the delayed
5 effect so they end up getting more proportional dose to
6 the amount handled because they were working over a
7 longer period of time.

8 MR. MILLER: And some of that might too
9 also be the, remember their default was half LOD and so
10 if you expect lower concentrations on the inner it
11 might also, I mean just the default could have been
12 partly the default values.

13 DR. HEERINGA: Cynthia Hines.

14 DR. HINES: Yeah. Just a couple of
15 comments. In your conclusion you stated that in some
16 cases it, you know, this proportionality may be
17 reasonable. But given what we had in our document, the
18 overview document from EPA and some of what you showed
19 today, do you have enough data to state that in some
20 cases this assumption is unreasonable?

21 MR. CROWLEY: I think you can make that
22 case as well.

23 DR. HINES: Okay.

24 MR. CROWLEY: But it's

25 DR. HINES: You kind of stated the more

1 positive picture here and I think there is some
2 evidence that in some cases it may be unreasonable.
3 But that needs further exploration.

4 MR. CROWLEY: And I guess the question is,
5 is our current, are we able to do that with our, make a
6 definitive determination

7 DR. HINES: Right.

8 MR. CROWLEY: with the current data
9 set?

10 DR. HINES: Right, that was why my concern
11 is, do you feel you have enough data yet to make that
12 statement? I might also comment that you very well
13 might find substantial colinearity between the amount
14 of active ingredient handled and exposure duration as
15 well. Those often go hand in hand.

16 And my last comment is I find the idea of
17 perhaps looking at seeing whether some of these
18 scenarios can be combined is intriguing and maybe
19 that's something the new data collection effort in the
20 Agricultural Handlers Task Database will maybe be able
21 to contribute to that. So that would be an encouraging
22 thing.

23 DR. HEERINGA: Dallas, Doctor Johnson.

24 DR. JOHNSON: Would you mind putting up
25 your slide 20? Thank you.

1 MR. CROWLEY: Would you like me to go to a
2 particular characteristic of the data or is this fine
3 right here?

4 DR. JOHNSON: Well if you could back up to
5 where you didn't have all the extra stuff on it.

6 MR. CROWLEY: Okay.

7 DR. JOHNSON: There, that's fine, thank
8 you. This is probably the only one that I recall in
9 which within a particular study there was a fairly
10 decent range of amount of ingredient handled. The
11 yellow dots, there's a little bit of a range in the
12 amount of ingredient handled and in the red x's there's
13 a little bit of range in the amount of ingredient
14 handled.

15 MR. CROWLEY: Yep.

16 DR. JOHNSON: And if you look at the
17 slope, if you were to fit a slope through the yellow
18 lines and you were to fit a slope through the red x's,
19 those slopes would be quite different. And neither
20 one, well, actually the one through the yellow might be
21 closer to having a slope of 1.

22 MR. CROWLEY: Yeah.

23 DR. JOHNSON: And the ones through the red
24 x's would have a slope much, much greater than 1. And
25 then if you would also put on the slide 19. In this

1 one here there's really no range at all within any of
2 the studies in terms of the amount handled. It's
3 basically the same for all workers and at least in the
4 proposed new data there will be, I understand there
5 will be some range that you'll try to achieve which
6 would be very helpful to try to assess whether the
7 slope is equal to 1 or not.

8 The other point, or a question I guess that I
9 have and maybe we're not, you don't have to answer it
10 yet is, why do we even care whether the slope is
11 greater than, equal to 1 or less than 1? Why not use
12 whatever the slope is? I'm not sure I understand the
13 rationale for looking at the exposure as a ratio of the
14 amount of ingredient handled.

15 MR. MILLER: Yeah, basically, I mean I'll
16 start and then if Matt wants to add such, this
17 basically the slope of 1 essentially equates to
18 essentially a proportionality of unit exposure. And in
19 essence what we do is we, that's essentially a
20 principal part of how we do risk assessments.
21 Essentially it's you take the unit exposure which
22 essentially is milligrams per pounds AI handled and
23 then multiply it by the pounds AI handled as part of
24 the equations that were showed, that were shown
25 earlier. So the question of whether it's proportional

1 or not essentially gets to whether that multiplication
2 of pounds AI handled by milligram exposure is a valid
3 way to go.

4 DR. JOHNSON: And what do you intend to do
5 if the new data shows that it's not proportional? At
6 least not proportional with respect to a slope of 1.

7 MR. MILLER: What we'd probably do is
8 start looking at other, as Matt had mentioned before,
9 other aspects that might be included. For example the
10 couplings was one of the things. It may be that
11 that's, if you have a close system it's not the pounds
12 throughput that goes through it but rather the number
13 of times you connect it. We would take a look at kind
14 of other things that might explain it. But again I
15 think our thought is that the new proposed data to be
16 collected by the HTF, I mean that is one of their
17 secondary objectives, to look at that and they'll be
18 collecting enough of that ancillary information for us
19 to look at various things like that.

20 DR. HEERINGA: Questions or comments from
21 other panel members? Yes, Cynthia Hines.

22 DR. HINES: I just had one quick thought
23 to follow up with what you were just saying. I know in
24 the AHETF's proposal that they're going to try and get
25 good variability on the amount of active ingredient, so

1 that will help you evaluate this proportionality. If
2 it should be the case that it appears some scenarios
3 that that's not a good normalization unit or measure
4 and say you wanted to look at a number of couplings or
5 a number of tank loads or something like that, the
6 current proposal isn't really designed per se to
7 optimize that variability or maybe that's something
8 that the task force can comment on. So if it's not
9 designed to optimize that, it may limit your ability
10 within that database to evaluate that. It's just a
11 thought.

12 DR. HEERINGA: Steve Heeringa, I have a,
13 if we could go to slide 18 and this is just an
14 observation. This whole discussion, and I think your
15 approach to test this assumption of proportionality is
16 correct, but it forces a linear model on this data over
17 a wide range of exposures and I think Dallas was sort
18 of getting at that earlier with slide 20 in which you
19 have two nice sets of data, probably the nicest sets of
20 data we have for this exercise.

21 If you wanted to write a textbook, Dallas
22 might use it. But the real world looks more like slide
23 18 and did you look at a quadratic term in this over
24 this range of exposure? I mean in my eyeballing of
25 this I would sort of, I would draw a quadratic function

1 through these data.

2 Secondly, this limit of detection of limit of
3 the quantification and sort of staking these below LOQ
4 values at a constant and then incorporating them in a
5 regression, you know, economists deal with this problem
6 in income and other types of things where you have
7 censored data and you might want to actually, as you
8 pursue this work here, maybe I'll just ask, have you
9 looked at things like, you know, censored regression, a
10 tobit regression in which you assume this lognormal
11 distribution continues uninterrupted or in a smooth
12 fashion below the limit of quantification, but you
13 don't stake the actual values at a point value at 50%
14 of LOQ. Did you do any of that work, Matthew or David?

15 MR. MILLER: We haven't done that in
16 relation to the, I mean it's something we plan to do,
17 it's something we've not done in relation to this
18 specific SAP. We do do that however on the residue
19 chemistry side, I've started using it.

20 DR. HEERINGA: I knew that you might do
21 that.

22 MR. MILLER: Yeah.

23 DR. HEERINGA: Do you see it making any
24 difference when you do that in your modeling in the
25 pesticides databases? Residues databases.

1 MR. MILLER: In the residue databases I,
2 let me think for a second, yeah, I mean you get, we use
3 essentially maximum articulated procedures to do that.
4 In terms of the estimates of the slopes, yeah, I mean
5 it can if you end up with a lot of 20% non-detects or
6 so. But I mean it's something we will probably at this
7 stage kind of look at in terms of this data here, take
8 a look at it. And certainly I think the more important
9 part is we'll be mindful of that with the AG. Handler
10 Exposure Task Force, their proposals. If their,
11 essentially if their detection are low enough that they
12 don't, they're less likely to cause issues or problems.

13 And then I guess on the first question you
14 asked which was in terms of we did not test quadratic
15 terms on this. We had discussed however that it may be
16 that if the equipment varied, just to look at this one
17 for example, if the equipment one uses at 100 pounds,
18 is that, yeah, at 100 pounds is different from that at
19 1 pound for example, that might explain essentially
20 kind of a disconnect there and we're talking about
21 doing potentially tests to look at that. I mean one
22 would be to put it in a quadratic term, or in other
23 words a Chow test, things like that. So that's
24 something we're aware of and we're thinking about and
25 as we look more into it it's something we may include.

1 DR. HEERINGA: Thank you very much. Other
2 questions from the panel at this point in time? Let me
3 ask a question of the Handlers Task Force.

4 Doctor Landenberger, Bryce, do you expect
5 your presentation to run say 30 minutes or no. Okay
6 well let's, before the break then let's proceed then to
7 the next component of the presentation for this morning
8 and that is a presentation from the Agricultural
9 Handlers Exposure Task Force on the statistical basis
10 for the AHETF data development program. And I'll
11 invite up Doctor Bryce Landenberger, Curt Lunchick and
12 Larry Holden.

13 DR. LANDENBERGER: Let me clarify.

14 DR. HEERINGA: Okay.

15 DR. LANDENBERGER: I misunderstood,
16 there's actually two different components to the
17 presentation. My particular component will not take a
18 half an hour however

19 DR. HOLDEN: It would be out of sequence.

20 DR. LANDENBERGER: -- it would be out of
21 sequence in terms of Doctor Holden's presentation

22 DR. HEERINGA: Okay.

23 DR. LANDENBERGER: should go first and
24 his is considerably longer than a half hour.

25 DR. HEERINGA: Is it longer than 45

1 minutes Doctor Holden?

2 DR. HOLDEN: I could talk faster.

3 DR. HEERINGA: Well that's what I don't
4 want to do to you but I'll tell you what

5 DR. HOLDEN: It's hard to say, it might
6 be 45 minutes might be more reasonable yes.

7 DR. HEERINGA: Let me, let's just go
8 ahead, it is only 20 minutes of 10:00 and if you'll
9 permit, if we feel that there is a breaking point, the
10 presentations and collection will certainly go longer
11 than 45 minutes or an hour so if you'll permit we may
12 find a logical breaking point and come back. I don't
13 want you to rush and I also don't want to interrupt at
14 a point where we would lose track of where we are but I
15 think it may make sense to proceed at this point and
16 we'll find an appropriate breaking point. Thank you
17 very much. This is Doctor Larry Holden I believe.

18 DR. HOLDEN: Can you hear me, oh great.
19 Oh, thank you. My name is Larry Holden, I'm a
20 statistician working with Silken and Associates and I'm
21 also involved with the Agency Task Force, I mean not
22 the Agency Task Force, I'm sorry, the AHETF Task Force
23 to help with the statistical and both analysis and
24 design issues. I apologize if my voice goes in the
25 middle of this, I'm fighting a cold and so if I start

1 sounding like the Cookie Monster you just have to
2 listen a little closer.

3 This talk that I and my colleagues are doing,
4 my talk originally was supposed to be together and
5 would include both the introduction to the design, I'm
6 sorry, to the study and the issue of normalization and
7 then followed by the sampling and sample size issues.
8 However it make it much more logical because of the
9 charge questions on sample sizes on the second to split
10 the talk.

11 However what I will do and I hope I remember
12 to do this, is that when an issue comes up with regard
13 to normalization or some other aspect that will be
14 talked about again or covered or maybe revisited at
15 least tomorrow I'll try to mention that fact and bring
16 forth any issues that might be relevant. So I hope
17 I'll remember that.

18 My presentation is really in three sections
19 and so a break could be in any one of these, Doctor
20 Heeringa, if that works out for you as well if it gets
21 too long.

22 The first two sections are more introductory
23 in a sense and the last section involves more about the
24 issue that was just discussed. The first section of
25 the talk basically describes the target population that

1 their study, pretty much the target population that our
2 study seeks to address. The second portion is going to
3 address the issue of where the Task Force's study falls
4 within sort of the spectrum between say a purely
5 descriptive versus an experimental approach. You can
6 probably guess from the discussions here it's more
7 towards the former than the latter. And finally we
8 want to discuss or describe briefly how this issue of
9 unit exposure is incorporated into our study and what
10 impact it has. And again some of the panel members
11 have already anticipated me already. They were
12 discussing, the previous speaker.

13 The pesticide handling scenario has been
14 described before by Doctor Canez and the definition is
15 here, I won't repeat it except to say that it is a
16 composite of many, many different things that are going
17 on but all have some commonality. So it's not as
18 though it's identical like in a controlled experiment,
19 it's a mishmash of many different things but they are
20 tied together in some, by some common framework.

21 Just to be a little easier, not a little
22 easier, at least a little simpler from a statistical
23 standpoint I'll try to put this in a little more
24 perspective so we can sort of lay the groundwork for
25 the sampling aspect later on. If we think of the whole

1 universe of all these conditions of which this scenario
2 comprises, what we're talking about is looking at
3 specific conditions or elements of this universe of
4 what's considered a scenario. And so what I've got
5 represented here is just a box representing some
6 arbitrary scenario and three example conditions that
7 are in this scenario. When I just say condition I'm
8 talking about something maybe more than most of you
9 realize, I'm thinking of every possible value for every
10 possible parameter that could affect exposure. So
11 clearly most people aren't going to have the resources
12 to investigate all that but that's what I'm talking
13 about when I'm mentioning a point in this box here.

14 The, I do want to clarify it because the
15 issue will come up in my colleague, Bryce Landenberg's
16 talk afterwards dealing with inter-person variability,
17 is that what we're, we're not saying that each point
18 here represents an individual, each point in this
19 universe represents a set of conditions of which the
20 individual is only one part of. And so an individual
21 might have in this example here several different,
22 represented many different times depending on the
23 different kinds of conditions he or she can experience.
24 And those conditions might even be differences in
25 behavior.

1 What I'm showing here is that if you knew all
2 those conditions you might be able to, that would, if
3 you knew some sort of the, if you knew the function or
4 the mechanism perfectly you might be able to predict
5 the exposure that went with it. Even though members of
6 this panel are probably more experienced in getting at
7 this function g than most, I'm sure that even they
8 probably can't specify this exactly. At least I'd be
9 surprised if they can.

10 There are, and so this looks very
11 deterministic here and I'm saying that there are known
12 factors and unknown factors that determine this
13 condition. But if you knew these and knew how they
14 were related I suppose you could come up with an
15 exposure and so it's not so important here now whether
16 they're talking about actual exposure or measured
17 exposure. But if you want to think of it in terms of
18 measured exposure then think of some of those factors
19 as being what influences the measurement as well. So
20 say an analytical error for example might be part of
21 that.

22 The reason I bring this up is it's going to
23 enter, it's going to come into play a little bit later.
24 But the diversity of the factors or the conditions
25 within this scenario universe all throughout, and they

1 are mapping into an exposure is basically going to give
2 you a distribution of exposure and that's because many
3 of the conditions might produce an exposure that is say
4 are closer together than some others. So it's going to
5 produce what I'm calling a distribution. And if you
6 look at those exposures that those conditions generate,
7 that is what our study is attempting to get at.

8 In other words every monitoring unit, every
9 sample that we collect and monitor hopefully is a
10 member of this universe although the reverse is not
11 necessarily true. What we do is we restrict our target
12 population somewhat from that universe and that's
13 restricted in some of the obvious ways that you see
14 here that Doctor Victor Canez talked about earlier,
15 that we limit our, we're only talking about
16 occupational agricultural handlers thank you very
17 much the, we always talk about workers with some
18 prior experience, at least 18 years old, in good
19 health, English or Spanish speakers, some of these
20 considerations are restrictions for a practical reason,
21 many are for ethical reasons, legal reasons.

22 There's also restrictions that don't really
23 necessarily apply to the workers, but to the
24 conditions. For example you've heard yesterday or the
25 day before that we are restricting it to, they have to

1 be at least a half day's worth of work for example
2 before that, they entered into our study. So we aren't
3 talking about someone who works 15 minutes.

4 We also are, the workers have to follow the
5 Worker Protection Standard. The application rates have
6 to be legal. So there are many restrictions, some of
7 those are implicit, some are explicit.

8 I think it's important to keep in mind what
9 those are because if one were to, one could always talk
10 about generalizing to the target population but if you
11 generalize to the entire scenario universe you have to
12 use something more than statistics, you have to use
13 subject matter knowledge. I think the gentleman right,
14 Doctor Hughes is it? Yes, you had mentioned the idea
15 of generalizability I think the other day and that's an
16 important concept is that to be able to generalize you
17 need to keep in mind the target population and what it
18 doesn't include. So I think that's very important.
19 And I think some of the panel members mentioned that
20 earlier.

21 What I'd like to get at quickly now is to
22 explain how our study fits into sort of a rough
23 spectrum between purely descriptive studies and say
24 experimental studies or non-experimental and
25 experimental. These, this isn't a very fine sharp

1 distinction, it's really more of a spectrum I guess you
2 would say. But nevertheless I'm going to try to
3 describe both extremes and then show where ours fits in
4 and why it fits in there. And that gives, and that
5 means that some things it can do and some things it
6 cannot do. Both of these approaches by the way I
7 consider are valid and very useful but they do have
8 different goals and limitations.

9 The descriptive viewpoint is one in which
10 this complex function I think of factors that determine
11 exposure can be viewed as something a little novel if
12 you want to call it by something a little simpler, and
13 that is that we're saying exposure might be
14 approximately equal to some measure of central tendency
15 and I mentioned the geometric mean here just for
16 convenience and some components that we're calling
17 random or treating or thinking of as random.

18 The reason I've got these as multiplicative
19 for those who are worried about that or concerned about
20 that is that you might normally be seeing this
21 additive. Most of the data that we've been working
22 with seems to be at least logsymmetric if not
23 lognormal. And it's more convenient to think of the
24 errors as being, or the random effects being
25 multiplicative. But if it does both you just think of

1 the log of it and it'll be additive again.

2 In the descriptive, at least how I'm viewing
3 it, I think the focus is more on describing the
4 expected variance of the worker exposures. And may
5 their location, but certainly the variation and the way
6 in which various statistics, the random effects and I
7 do mean that to be plural because those effects don't,
8 are not going to necessarily seem variable, they're a
9 mishmash of many things that are modeled but necessary,
10 not necessarily modeled independently.

11 That, the variability of that tends to be in
12 this kind of approach, it tends to be very, very large.
13 And in our studies we're talking about geometric
14 standard deviations for those of you who think in those
15 terms of around 4 which is, for those of you who deal
16 with coefficients of variation we're talking around
17 250% as opposed to maybe an agriculture where they're
18 dealing with CVs of 20%, 30% maybe as being minimal.
19 For those of you who like to think in terms of orders
20 of magnitude we're talking two, two and a half orders
21 of magnitude between the observations. So a large
22 variability there.

23 But in other words in this kind of study, at
24 least how, the extreme in which we're talking about
25 this descriptive of the individual observations, it's

1 the distribution that's of interest and for example the
2 Agency has already brought that they want to look at
3 things like the mean and upper percentiles of this
4 distribution for use in risk assessment.

5 The experimental viewpoint, or at least how,
6 you know, on the extreme side is one in which we have
7 the same function controlling things but we're
8 approximating it by some simpler function of known
9 factors and also random variability goes along with it
10 as well. However in this case the random variability
11 is more of a nuisance than it is something in which to
12 describe.

13 It's something we would like to, and ideally
14 get rid of or reduce to as low as possible and explain
15 things in the, in whatever function of some known
16 factors, because in this case it focuses on discovering
17 relationships between known factors in exposure.

18 Not to say this can't also be done in a
19 descriptive standpoint as well but it's more,
20 oftentimes more a better approach to an experimental
21 viewpoint, especially since in order to get at this
22 function in an ideal situation what you'd like to do is
23 experimentally vary some of those known factors and how
24 as many of the others as possible as constants and
25 unfortunately throw maybe some of the rest and those

1 you don't know and treat those as error. But you still
2 want to minimize that. The useful for this is that
3 it's very useful for predicting exposure for a
4 particular set of conditions, useful for discovering
5 the relationship, at least conditional on things you
6 hold constant. But it will destroy, by design, any
7 natural co-occurrence of the factors that may occur in
8 the population and that's a good thing in an
9 experimental study, that's what you want to do.

10 But our program really is focused more on the
11 descriptive I think than the experimental and I wanted
12 to emphasize this, especially because it's very easy to
13 get off into thinking that this study can look at all
14 different factors and compare things and look at the
15 relationship between this piece of equipment and that
16 piece of equipment, this factor and that factor and you
17 soon run out of sample size very quickly in that
18 approach. And we're not really getting at that
19 approach. I just wanted to specify that, we're not
20 really necessarily concerned with how well the data
21 could undercover relationships, although as you'll see
22 we do a little bit of it.

23 In general I think it's pretty obvious why
24 you proposed the approach but for more obvious reasons
25 than not, exposure measurements are, if you manipulate

1 them in situations where that's not necessarily typical
2 and manipulated conditions, when you're trying to use
3 it to describe the distribution it's going to be
4 misleading because you're, you've got conditions that
5 don't necessarily occur very often if at all. The
6 natural distribution however is something that can be
7 used directly for, as you've mentioned, tier 1
8 assessments. To get at that distribution from an
9 experimental study means you have to throw in
10 assumptions, additional assumptions but the
11 distributions of the things that you used in the
12 experiment.

13 So it becomes more complicated at the very
14 least. And it's also complicated to design the
15 studies. Remember now, our, the Task Force's study,
16 we're not doing an experiment, doing a study and plan
17 to analyze the data and publish it. We're generating
18 data for others to use. They will be used either in
19 regulatory purpose or perhaps in publications of their
20 own or whatever. So to try to design a study to
21 anticipate all the possible ways in which a, potential
22 users could use data and what kind of relationships
23 they may want to find is going to be not only very
24 complicated but could result in very, very large sample
25 sizes if we try to accommodate everyone, every possible

1 use.

2 But, after saying this, and I think Doctor
3 Heeringa, no I'm sorry, Doctor Portier was discussing
4 yesterday, the day before, I can't remember which,
5 about all the factors in which the, all the
6 measurements in which the study would be taken, would
7 be measured, we're going to be measuring a lot of
8 factors that go along, I mean, almost as, very, very
9 many, a large number, so those are going to be
10 available.

11 So users, there's nothing stopping users of
12 this database from running regressions on as few or as
13 many factors as they wish, but we have a caveat here
14 that many of these factors are very highly correlated
15 and I think you mentioned that earlier on that, today,
16 that they're highly correlated.

17 Time for example, pounds per AI handled are
18 highly correlated. And certainly in the scenario
19 universe, and since we're trying to collect data that
20 mimics it to some extent, then that, our sample is
21 going to have the same kinds of correlations in it if
22 we're doing a good job. And because of that you've got
23 this multi colinearity issue or confounding, whatever
24 you want to call it, and why you might be able to use
25 other normalization factors for example, you are not

1 going to be able easily to maybe distinguish one factor
2 from another or perhaps use them jointly because as the
3 statisticians know quite, you run into problems really
4 fast. And Doctor Johnson who taught me messy data
5 analysis I'm sure knows this quite well.

6 Some of the problem situations, I've already
7 mentioned a couple but some of these factors that are
8 obvious, that amount of AI handled is going to be
9 highly correlated with the number of loads, hours
10 worked, acres treated, spray volume mixed. There are
11 going to be some factors that don't vary that much, are
12 hard to vary and some of these might do with factors
13 that are behavioral that are very, very hard to control
14 anyway. And so they're going to come out to be
15 correlated in the data.

16 So the bottom line is there's not going to
17 be, we're not going to, the Task Force is not going to
18 be able to guarantee that AHED data can be used
19 successfully to discover factors that influence
20 exposure. The data is going to be available and
21 therefore we're going to try but there's not going to
22 be any guarantee, it's going to be limitations.

23 But, and I'm always throwing out a but, and
24 here's another one right here. There is one factor
25 that is recognized as being very important, we've been

1 talking about it today especially, and that is the
2 amount of active ingredient handled by a worker during
3 the daily task. I think it's, I'm not going to beat a
4 dead horse into the ground, but it's obviously
5 important. It obviously, and I say obviously because
6 even some of our data that we've examined shows that it
7 is, it is associated with exposure, not necessarily the
8 same day, it's always proportional.

9 Although to be fair, every data set that
10 we've examined so far has shown that is proportional
11 within the context of our data, or that our data are
12 incomplete and unable to distinguish whether it's
13 proportional or not, we can't make a conclusion.

14 So us, the Task Force as of right now can't
15 go out on a limb and say that we have evidence to say
16 that for scenarios it is not true, we have evidence to
17 say that it is true in some cases and we have, our data
18 shows that it's equivocal in others.

19 But in reality, and I think someone here
20 suggested it, if you know that you go down low enough
21 you're going to be picking up background that's going
22 to flatten out, if you go high enough, pounds per AI
23 handled, stuff, Doctor Pependorf and I were talking
24 earlier this morning, things are going to be falling
25 off left and right. So we know that it's going to

1 flatten out on both ends if you go far enough, so at
2 the very least it's going to be a sigmoidal at the very
3 least, although it'll be more complicated in between.

4 In particular though, because the Agency and
5 others are interested in normalized exposure or unit
6 exposure, the two will be synonymous, then we are going
7 to look at that in our study as well. It's going to be
8 like an add on, or it's going to in a sense, even
9 though we're collecting data we're going to orient to
10 try to maximize the information we pick up from this
11 one parameter.

12 Like exposure, we can also think of
13 normalized exposure having a distribution too. There's
14 nothing, any parameter in that, any measurement, any
15 one of those factors that exist or a combination of
16 factors can be described by data. So you could think
17 of normalized exposure just like exposures having a
18 distribution and then you could look at it to say the
19 mean of normalized exposure multiplied times pounds per
20 AI handled and come up with an estimate of a, the mean
21 of exposure conditional on a given amount of AI
22 handled.

23 Likewise with the percentile. These are the
24 ways in which the regulators for tier 1 and maybe tier
25 2 assessments tend to use the data. And as I said it's

1 always meaningful to describe the distribution or at
2 least doable to describe the distribution of normalized
3 exposure in the data. Nothing wrong with that. But
4 for it to be useful, be useful for predicting exposure
5 at a given level of pounds per AI handled, I'm sorry,
6 amount of AI handled, make s a further assumption, an
7 obvious one, and we've talked about it earlier today,
8 that apart from "linear effects", exposure is
9 proportional to amount of AI handled, excuse me.

10 Of you write it like I've got down here at
11 the bottom that exposure is approximately equal to
12 amount of AI handled times some constant
13 proportionality, times all your random effects. If you
14 do that, if you write it that way and look at it that
15 way, then this is what we've seen in Doctor Crowley's
16 presentation or Matt's presentation, you end up getting
17 a line, a linear equation that's in terms of log, with
18 log exposure is related to the log of pounds per AI
19 handled with a slope of 1 plus some additive there on
20 this log scale.

21 So if you believe that that previous
22 relationship is true then of course you've got, you
23 have a relationship like this and do you have a
24 pointer by any chance thanks. How do you work this
25 thing?

1 SPEAKER: Just push the button.

2 DR. HOLDEN: Oh, a button, my gosh,
3 technology. I'm used to using my computer mouse.

4 I wanted to use this slide because it's a
5 great opportunity to comment on some of, some of the
6 conversations I've had about this earlier and also the
7 talk that we just heard from Matt Crowley. Doctor
8 Pependorf and I were just talking earlier today and he
9 pointed out correctly that there's a lot of things
10 assumed in this, even if you don't assume one, but a
11 lot of things that are assumed in this equation that
12 are tricky.

13 One of the most obvious things or one of the
14 most important things is that you notice that we've got
15 this random hump back there which includes a whole mess
16 of evils and there are many factors in there in which,
17 probably also have exposure as well as pounds per AI
18 handled. We don't know what they are necessarily. And
19 in addition there are many factors in here that
20 probably are in some sense associated with pounds per
21 AI handled in there. So at best what this represents
22 is what I call a marginal relationship. In other words
23 it's the, it's the best all you can hope for is that
24 this relationship is linear or linear to the slope of 1
25 averaged over everything else that can affect exposure.

1 So that's the best you could probably hope for.

2 And that means that we saw a lot of these
3 studies, a lot of the results previously and when you
4 have one study over here at the top say the high pounds
5 per AI handled and another study down here, that there
6 are many, many, many different things that vary between
7 that besides pounds per AI handled.

8 Some of those things, we know what they are,
9 many of them we have no idea what they are, at least
10 have no idea what affect they may have. And so you've
11 got an extra variability due to those things that the
12 simple regression equation doesn't recognize. And so
13 it's going to declare things as being significant or
14 non-significant if you don't account for those factors.
15 Now, Matt did account for those factors in his high
16 model analysis, at least accounted for them to the
17 extent that you could given the data that he had. And
18 that's a fair statement.

19 In our studies we are attempting to spread
20 out, and I think as Jan said over here, we are
21 spreading out our pounds per AI handled as much as
22 possible within a study so that when we do have
23 separate they, there's a degree of overlap. And in
24 addition when that's impossible or we have the margin
25 of data that have, already existing that perhaps don't

1 have such a wide range we try to get as many studies as
2 possible and as many pseudo data points as you possibly
3 can.

4 And the final thing I want to mention here is
5 that if you focus say in one small area of this plot,
6 in other words you restrict the pounds per AI handled,
7 very small, you can see or maybe it's very difficult to
8 see but if you squint your eyes or put your fingers in
9 front of the plot, that you no longer see that linear
10 trend.

11 In other words if you focus on too small a
12 range you can't tell whether it's linear or not. As a
13 matter of fact you can even have a reversal. You can
14 look at this points here and these points over here, it
15 might look like you've got a result going this way if
16 you focus on too small a range. And that means that
17 the range of the x variable here is very small relative
18 to the range of the variable, the r variable. So it
19 looks like a shotgun on that level. So it's, you're
20 taking a lot larger sample sizes to be able to revolve
21 that.

22 So again it's important because that's going
23 to come, that's going to be reflected in what we're
24 talking about tomorrow versus sample size and design
25 with regard to how wide this pounds per AI handled

1 range might need to be before certain things are
2 possible.

3 Now that I've said all of the things that
4 could possibly be wrong with data like this, or at
5 least all the complications, if it is true and if this
6 relationship turns out to be true, and this answers
7 Dallas' question I think, or gets to it, then if you
8 look at the exposure per pounds AI, the normalized
9 exposure on the x axis you should have no relationship
10 or no discernable one on the amount of AI handled.

11 And if that's the case you could sample, take
12 a sample of data and use it to predict a distribution
13 of normalized exposure which would be identical,
14 mathematically equivalent to, as the predicted exposure
15 distribution assuming the amount of AI handled is equal
16 to 1. Then you could use that, superimpose it upon
17 the, this proportional line where the slope equals 1 on
18 the log scale and in a sense get an idea, it says
19 accurately predict, but let me say you'd get a, only to
20 the extent that any sample could accurately predict,
21 you'd get an idea of what the distribution might be.

22 So the bottom line is if the normalization,
23 the proportionality is true, then it's very easy to see
24 what you can do with the data, you can make some
25 simplifying assumptions. If it's not true then these,

1 this use is no longer necessarily valid although it
2 might still be approximately true or it might be with
3 assumptions. It could be used conservatively, but
4 nevertheless that's the rationale for this.

5 Now, to start closing down here, as a result
6 of its importance, this parameter, I said before the
7 monitoring program that we're going to be using will
8 focus, for the purposes of sample size, it's the
9 benchmark adequacy goals on normalized exposure. In
10 other words we're going to use this interest in
11 normalized exposure to a certain extent to help us plan
12 the sample sizes.

13 I want to emphasize that the study does not
14 assume, we do not assume that normality is true, I'm
15 sorry, normality is true, we do assume that
16 proportional relationship is true, we do not assume
17 that any relationship is true, or any other.

18 What we are saying however is that we can
19 only design the study to optimize for certain things.
20 And so because there is so much of an interest in using
21 this we are going to use that in helping us design the
22 study.

23 In one sense we're going to use, and we'll
24 address this detail tomorrow, but right now let me just
25 say that we are going to use the, we are going to ask

1 that the study be a sufficient number of replicates and
2 clusters and whatever else so that the distribution of
3 normalized exposure, which means that we get
4 information about that distribution in advance as much
5 as we can to help plan sample sizes that that'll be,
6 have some degree of accuracy, some degree of precision
7 accuracy with respect, and we'll discuss in detail what
8 that means tomorrow, but we're going to use that as a
9 benchmark criteria, not to say that that's the only
10 thing we'll be doing with the data, but we will in some
11 sense have assurance or guarantee that the user could
12 use it for that purpose.

13 And in addition we are designing the study
14 and you've already seen how we're doing it by spreading
15 out the pounds per AI handled in such a way to
16 hopefully ensure that some limited examination of the
17 relationship between AI and exposure can be addressed.
18 When I say limited I doubt seriously whether a user is
19 going to look for a complicated function of pounds per
20 AI handled.

21 Maybe as Doctor Heeringa said, a quadratic or
22 something may be possible to be able to see something
23 like that or as Matt Crowley talked about, using that
24 data to look at different slopes which effectively you
25 do a simpler spectrum between complete independence.

1 In complete proportionality there's something in
2 between which has this curved linear aspect to it.

3 And so certainly the study will enable, the
4 power is going to be, is really going to be limited,
5 the power specification is going to be limited but it
6 will have some criteria for that. And that's pretty
7 much the extent to which we're assuming or we're using
8 the unit exposure concept in our study. So it is
9 designed to get a large number of variables as you saw
10 so users can do any normalization they want and as
11 someone pointed out, because variables like time, say
12 for example, tend to be correlated with pounds per AI
13 handled, the adequacy for normalizing based on pounds
14 per AI handled can probably be done on some other
15 factor like time as well because it's going to be
16 varied in that database as well. So you'll have that
17 but in all cases it's going to be a marginal
18 relationship that can be tested.

19 And finally let me close with, well, almost,
20 next to last close anyway, that you might, because
21 we've moved our, we've allowed a looking at, or are
22 going to move the study a little bit to try to get an
23 examination of pounds per, amount of AI handled, we are
24 looking at one factor. So if you think of it as being
25 this little, if you think of this spectrum that we

1 mentioned from complete descriptive where all you're
2 looking at is the variation down to complete
3 experimental where you're looking at a large number of
4 factors, we've moved our study down a bit, not halfway
5 between the two but a little bit towards the experiment
6 in the fact that we're looking at this factor.

7 Although some people in the description of experimental
8 may argue correctly so, that we're, we, you can still
9 have a descriptive study and look for functions but
10 because we're manipulating the factor it's getting
11 closer towards experimental. But I just want to
12 emphasize that that's about the limit of what we're
13 going to be able to do I'm afraid.

14 In summary then let me say that the target
15 population as I've described for a scenario is a little
16 bit different than the totality of what's in the
17 scenario for many different reasons, and I think it's
18 going to take subject matter expertise to be able to
19 determine whether that can be generalized, if it even
20 needs to be generalized to the larger set of scenarios,
21 but I've heard many comments the last couple of days
22 that expressed opinions on that and all those have been
23 very helpful.

24 And in addition to the target population I
25 want to mention that it's not just the workers we're

1 talking about, we're talking about the target
2 population of traditions as well. Our monitoring
3 program as we said is more descriptive than
4 experimental and I think the emphasis, we have an
5 emphasis on exposure normalized by amount of the AI
6 handled but not a dependency. Thank you very much.

7 DR. HEERINGA: Thank you very much, Doctor
8 Holden. And I think what I'd like to do at this point,
9 we have additional presentations and I'd like to return
10 to questions on your presentation, let you give your
11 voice a rest.

12 DR. HOLDEN: Thank you.

13 DR. HEERINGA: Let's take a 20 minute
14 break and come back here at 25 minutes of 11:00 and
15 we'll resume with questions from the panel for Doctor
16 Holden and then continue on with additional
17 presentations, I guess Doctor Landenberger and Curt
18 Lunchick again.

19 So we'll see everybody back here at 25 to
20 11:00.

21 (WHEREUPON, there was a recess).

22 DR. HEERINGA: We still have a few members
23 of the panel who have yet to reappear so I'll wait
24 another minute before we begin.

25 Okay, welcome back everyone. I think Doctor

1 Portier and Doctor Chambers are still to arrive yet.
2 We'll wait just a minute.

3 While we're doing that I also wanted to
4 acknowledge at the table here, Doctor Tina Levine who
5 is the Director of the Health Effects Division, I
6 normally introduce each day. Welcome.

7 Okay, let's get underway now that we have a
8 quorum of the permanent panel members here.

9 Just before our break we heard a presentation
10 by Doctor Larry Holden, describing some statistical
11 aspects of the AG. Handlers Exposure Task Force
12 proposed database or AHEAD, I guess not proposed, the
13 AHED database. And we wrapped up without having any
14 sort of questions of clarification from the panel.
15 There will be several other statistical presentations
16 to follow from the Task Force, but I wanted to make
17 sure that panel members were clear with everything that
18 Doctor Holden presented, or if you have any questions.
19 Doctor Lu, Alex.

20 DR. LU: I think that Doctor Holden gave
21 an excellent presentation. I think the concept that he
22 provided I would say will be a wonderful doctoral
23 dissertation project. Seriously I think it's, I would
24 take his message with me home.

25 The question about a selective target

1 population, if you can go to slide 16, oh, this is
2 different. Well I can ask this question first. When
3 you say manipulating worker activities, could you
4 provide some real example of how we can manipulate
5 worker activities that's kind of deviated from their
6 usual practice?

7 MR. LUNCHICK: I think an example or
8 examples of this is to dictate specific types of
9 equipment that they would not normally use or to have
10 them, for instance they would normally be using
11 Chemprobes and we're going to want them to use a dry
12 break system which would have a significant impact on
13 the exposure. Our emphasis is to catch what is
14 typically used in the variable that we are going to
15 capture the widest variability on, of course it's the
16 amount of active ingredient handled.

17 So that's what it is, we're dictating their
18 work habits, we're trying to avoid that to the greatest
19 extent possible.

20 DR. LU: So in other words this can be
21 called misapplication. It's not applying pesticide
22 according to the label so it would be a misapplication.

23 MR. LUNCHICK: No, we would never under
24 any circumstance as them to do any application that's
25 not consistent with the label. But the label gives

1 great leeway. For instance the label may not prohibit
2 an open pour loading and a manipulation would be to
3 dictate in that case to use a closed loading system
4 which would cut out probably the predominant use of a
5 product that does not prohibit open pouring.

6 DR. LU: All right, thanks. So the target
7 populations, the equation that you presented, there's a
8 random variable term that you feel like you will
9 probably dictate the outcome of the data, right? And I
10 thought, I directly thought maybe that's why you want
11 to select a population to minimize this random variable
12 term as much as possible so you would totally diminish
13 the effect toward the end of the data analysis.

14 When I look at your criteria of selecting so
15 called target population, I mean what is the, how much
16 do they represent the total pesticide applicator in a
17 workforce? I mean I would say for example one of the
18 criteria is a non-pregnant woman. I don't know who
19 would actually be pregnant and then still go out and
20 spray pesticides. So are you talking about 90% of the
21 total workforce or the 9% of the total workforce?
22 Because I mean if it's really only 9% then that's a lot
23 of data deletion here.

24 MR. LUNCHICK: This is Curt Lunchick
25 again. This is background for everybody, as we go out

1 to collect data we very early on will begin to talk to
2 grower groups and others out in the field to make we
3 have a good understanding of the typical use patterns.

4 We have a subcommittee, AHAP, I don't
5 remember offhand what it stands for, I get acronym
6 overload too, but it's like tree growers, we'll deal
7 with, like if we're going out into the Pacific
8 Northwest to look at the apple growers, we'll get with
9 those people well beforehand to make sure we have a
10 good understanding of the agricultural practices.

11 In regards to restricting parts of the
12 population, the pregnant women is a necessity. The
13 number of people that are actually limited, probably
14 extremely small. There's no way we're ever going to
15 get an accurate percentage on that.

16 The English and Spanish, obviously that's the
17 majority of the user population but I think you get
18 into an area like Belle Glade, Florida where you have a
19 lot of Haitians, French of Creole speaking, right now
20 we would not hit that area. But if we found that it
21 was important, there was something going on we needed
22 to in that area, we would amend that type of
23 restriction to make sure we had a Creole speaker. But
24 in general right now that's our plan.

25 So we're trying to minimize the restrictions

1 and most of them are based on practicality more than
2 anything else.

3 DR. HEERINGA: Doctor Chambers.

4 DR. CHAMBERS: I feel compelled to put
5 my HSRB hat back on and I think it may just be, if you
6 can go back to that same slide, Larry, 16, it may just
7 be a matter of semantics but the term, manipulate,
8 raises all sorts of potential flags I think. And in
9 using that, you know, I understand what you're saying
10 there but again manipulate could mean that you're
11 asking people to be exposed to more than their normal
12 workday would be and I don't know whether that's what
13 you mean or not. As long as you're asking them to be
14 exposed to less than their normal workday I don't think
15 that's going to be a problem but if it's more it surely
16 will be.

17 DR HOLDEN: Of course in that slide that
18 followed a statement that that's what a experimental
19 approach might do, not what we're doing. Manipulating,
20 when you're, if you're doing an experiment, a designed
21 experiment, not a designed experiment but I also have
22 to go, not us, let's say someone else, they would have
23 to go through HSRB probably if it's done for regulatory
24 issues anyway. And the design, and they also obviously
25 then would not probably do exactly what you say, they

1 probably would manipulate so they increase exposure,
2 they wouldn't be allowed to.

3 But if it were an animal study, say, they
4 might choose to do that. An experiment would choose to
5 do things that would not normally be done in practice
6 for the purpose of delineating, maybe testing one
7 treatment versus another treatment or one condition
8 versus another condition.

9 So in this example I was saying we're not
10 doing that. I mean we're not, we're not doing
11 experimental approach. Yes, we are doing some
12 manipulations like pounds per AI handled obviously.

13 Is that what you meant or am I
14 misinterpreting it?

15 DR. CHAMBERS: Well it's just, you know,
16 the whole idea of there being some scripting of these
17 things, again there's going to be some flags raised if
18 this is going to likely expose people to more than
19 their normal work activity.

20 MR. LUNCHICK: Yeah, I, this is Curt
21 Lunchick again. After two months of preparing for this
22 and having my statistician here restrict me from using
23 words like proportional representative, replicate and
24 other words that I'm used to using because they have
25 statistical meaning that I'm unaware of, this is a case

1 of you using a term that has meaning, that has
2 implications beyond the experimental. And I think the
3 point is well taken. Because of the requirements of
4 the rule the term, manipulation, has connotations that
5 we have to be careful of too.

6 And obviously in any experiment, or not even
7 an experiment, any study that we do, they're not
8 experiments, but going out into the field and
9 collecting data, we go through a detailed informed
10 consent process for anybody who participates in our
11 studies.

12 So, but I think your point is well taken and
13 when we go to the HSRB our statisticians will have to
14 be careful on the terminology also.

15 DR. HEERINGA: Yes, Cynthia Hines please.

16 DR. HINES: I just have one comment. One
17 of the objectives that has been described on previous
18 days for the Task Force is to look at some of the more
19 modern handling technologies, both probably at the
20 mixing side and the application side. And it is
21 probably reasonable as was used earlier that there is
22 an association in most cases or in many cases between
23 pounds of AI handled and exposure.

24 I'm wondering once you start looking at some
25 of these more highly engineered mixing technologies if

1 that will hold true and if there is going to be an
2 ability within your data sets to get a handle on that
3 because after all, the whole idea behind that is to
4 minimize contact and perhaps you will have a different
5 picture?

6 MR. LUNCHICK: That's a very good question
7 and actually one we were hoping for, I hope I don't
8 steal Doctor Hamey's thunder with my answer. But
9 actually I wanted to put this in something of a
10 regulatory perspective and I think your question leads
11 to that.

12 We are using this proportionality between the
13 amount of active ingredient handled and the exposure as
14 an assumption to design our study. When sufficient
15 data come in and probably from multiple studies for a
16 give scenario, we will then analyze the data. And one
17 of the things obviously will be to see if the
18 assumption holds or makes sense. I fully expect that
19 when we get into sophisticated engineering controls,
20 enclosed cab vehicles with air purifying system, et
21 cetera, dry break loading systems where essentially
22 once you connect the hoses you turn the pump on and
23 whether 100 gallons or 10,000 gallons flow through,
24 probably it's going to be a minimal effect.

25 And yeah, so I think in those cases and in

1 every case, once we get the data in and start the
2 analysis we will be doing that jointly with EPA, PMRA
3 and DPR in reaching a consensus and a joint
4 recommendation based on the data to users of the
5 database.

6 DR. HEERINGA: Doctor Johnson.

7 DR. JOHNSON: Yeah, if you put slide 26 up
8 there. This is a nice slide and you have that
9 distribution whether the slope of that line is equal to
10 1 or not so I think it's not an assumption that needs
11 to be made and it sounds like from Doctor Lunchick that
12 you're not really going to make that assumption. And I
13 don't think it's an assumption that's necessary for the
14 various kinds of arguments that have been given so far.

15 DR. HOLDEN: This is Larry Holden again.
16 There is one caveat about that. You are right by the
17 way, we don't assume that the proportionality is true.
18 I know I keep saying this, it must be a force of habit
19 from the old days, we don't assume that the
20 proportionality is true.

21 We do assume it as a benchmark for the sample
22 size. But in this example that I gave here, this
23 illustration you can flip to the next, the previous
24 slide, yeah, this previous slide, if it's not
25 proportional then what will happen is that instead of

1 being a, with no relationship there it will actually be
2 higher at the left end and slope downward. And so if
3 one were then taking samples and plot that distribution
4 you would have something that would be bigger than what
5 it shows there because it would be incorporating the
6 variability plus the negative trend because of what
7 you're doing in that case. And so therefore your
8 distribution that you estimate would be bigger there
9 and then if you use that distribution and force it upon
10 the and unfortunately I don't have a slide for this,
11 I should have a slide for that then if you force that
12 distribution then what you'll have is, it'll look, you
13 know, fit exactly on there but now the data point's a
14 reality, it would be flat, they wouldn't follow that
15 line. Assuming it's, or maybe it, I'm assuming it's
16 independent as an example.

17 But the distribution would be very much
18 bigger so what you'd have then is something that really
19 over predicts the distribution at the high end and
20 under predicts it at the low end. I think David Miller
21 or Matt Crowley mentioned that during their talk I
22 think as well.

23 So it does make a difference. We're not
24 assuming this of course but in this example, what I
25 said on the usefulness, the usefulness of normalized

1 exposure, that usefulness has to be expressed with some
2 caveats if that doesn't hold true. Because what
3 happens is you're not estimating, not only are you not
4 estimating the distribution correctly, no, you are,
5 you're estimating the distribution correctly but trying
6 to extrapolate it to future, to regular exposure at a
7 given pounds per AI doesn't hold true. I hope that's
8 clear. In other words it, the distribution will go,
9 let's go back here, instead of looking like this,
10 whoops, suppose it's just flat instead, then if you
11 normalize it you'll get something that looks not like
12 this but higher up here and slopes down like that.

13 DR. JOHNSON: But the point would be that
14 you would look at the variability around whatever line
15 you fit?

16 DR. HOLDEN: Yeah and that, right, and
17 you're actually right.

18 DR. JOHNSON: That variability shouldn't
19 change.

20 DR. HOLDEN: Yes, I think your point is
21 well taken, I think what you're really saying is,
22 something that you mentioned earlier on, that if you
23 use whatever the data fit, show, and use that
24 distribution then you're home free except for, you
25 know, sampling error, et cetera, et cetera. But yeah,

1 that's right is that if you, the danger is if you
2 assume something that isn't true.

3 DR. JOHNSON: I think we're basically in
4 agreement.

5 DR. HOLDEN: Yeah, we're used to doing
6 this by the way, that's why.

7 DR. HEERINGA: Additional comments at this
8 point? I think we'll probably get back to the
9 discussion of that issue seeing the look on Dallas'
10 face, we'll probably come back there.

11 Okay, at this point I want to thank you very
12 much, Doctor Holden and I think there is a, the next
13 presentation from the AG. Handlers Exposure Task Force
14 on the topic of within worker versus, between worker,
15 is that what you're doing?

16 DR. LANDENBERGER: Yes, that's correct.

17 DR. HEERINGA: Doctor Bryce Landenberger.

18 DR. LANDENBERGER: As mentioned my name is
19 Bryce Landenberger and I am the technical leader for
20 the Chronic Risk Assessment and Statistics Group at the
21 Dow Chemical Company. I'm here today representing the
22 AG. Handlers Exposure Task Force but I also wear
23 another hat and I apologize if I get my Task Force
24 mixed up. I'm also part of the Antimicrobials Exposure
25 Assessment Task Force and have been since its

1 inception. In that capacity I make myself available to
2 the panel if they have any questions concerning design
3 or sample size issues related to the Antimicrobials
4 Task Force and some of the issues surrounding it that
5 differentiate from our AG. Handler colleagues.

6 With that, in my presentation today I'd like
7 to go over some basic things related to the intra versus
8 inter-worker variability and we're going to talk about
9 this with regards to some basic definitions and
10 concepts and we'll be looking at this in particular by
11 looking at the within worker correlation number. We
12 will look not only at what that general definition is
13 and what its general impact is, but look at what its
14 impact is on long term exposure estimation, how we
15 would get at an estimate of a particular parameter and
16 then some practical considerations for gathering that
17 data to estimate that intra, within worker correlation.
18 And I apologize if I mess up on my terminology, I keep
19 on stumbling over these terms myself all the time.

20 Let me start out with this first slide which
21 gives us some basic definitions. Up at the top we have
22 a distribution in gray on these slides here. And this
23 is basically the between worker distribution of single
24 exposures and this would be if you were just taking
25 particular individuals as represented in this box down

1 below the distribution here, and getting their values
2 of exposure over the different particular study and
3 then developing from that the distribution that we see
4 above. If we were to do repeated measures over days or
5 months or years on a particular worker, either those in
6 the green circles here or the red triangles, what you
7 have there is then the within worker variability.

8 Now, if we were doing just this top part and
9 we had repeated measures on individuals, that whole
10 variability that's considered there is what we are
11 calling the variation between workers, sometimes called
12 the total variation. It has two components to it. One
13 is the between worker component and the other component
14 is the within worker component. But it is important to
15 keep in mind that this is basically a total variation
16 estimate up here because we need that for our
17 definition of the between worker correlation. I
18 already got my terms mixed up.

19 So what, another thing I want to point out
20 here is these dotted lines would represent the means of
21 a particular individual long term. And this will be
22 important as we start looking at how do you go from the
23 data sets we collect in a single exposure and
24 incorporating that with the within worker correlation
25 to get an estimate of a long term exposure

1 distribution. Next slide please.

2 So the concept we want to have here, and I
3 apologize, this particular equation, RW equals $1 - W$ bar
4 over B , I noticed did not print out in the printouts, I
5 noticed that last night and there wasn't much we could
6 do about that. But this is a key equation that we have
7 here, a key concept with the within worker correlation.
8 And what we have if we look at this particular
9 distribution, the same place we started, again you can
10 see this over and over again in the slides, you have
11 the various workers here.

12 What we're going to do is if we had variation
13 within a particular couple of workers here we might
14 have that variation measured by W_1 , W_2 and in this
15 particular case the example shows these are fairly
16 small within worker variations. I think if you
17 remember what Matt Crowley presented this morning, in
18 some cases that appeared to be the case when they did
19 repeated measures on some individuals, in some cases it
20 was fairly widespread.

21 This particular example, if you take that
22 average of these variations and divide it by B , which
23 is labeled here, the variation between workers, but
24 remember it's also total variation, this will give you
25 a number between 0 and 1 for the within worker

1 correlation. And again, since this is small this ratio
2 will be a small number, it will be close to 1. And
3 that's basically what we're doing with this equation
4 here. And this is the concept again, the within worker
5 correlation that we want to deal with. Next slide.

6 On the other hand if we had a particular
7 individual and their variation was quite wide, W_1 is
8 going to be wide and if you had similar results for all
9 of these individuals up here, $\bar{W}$ is going to be
10 fairly large, that average within worker variation. So
11 this ratio is going to be fairly large and R_{WW} is going
12 to approach zero. Again, keep in mind that the
13 variation up here between workers is total variation.
14 Next slide please.

15 So what is the impact of this particular
16 approach to this and looking at the within worker
17 correlation? Again if we have this distribution up
18 here and you have these individuals here, each one of
19 these workers, if we had repeated measures we're going
20 to be looking at their averages, essentially their
21 averages as we're looking at a long term exposure.
22 This might be something over a lifetime as we have
23 examples down here.

24 So we would be looking at that particular
25 exposure, the cumulative exposure for that individual

1 would be the worker mean times the number of exposures.
2 For example if we had the units in milligrams per
3 kilogram per day times the days of exposure over this
4 entire range here, that would give us their cumulative
5 exposure. So as we look at this, RWW is a way in which
6 we can progress from the short between worker
7 distribution of the single exposures and get down to a
8 long term exposure. But we need to keep in mind that
9 this particular distribution at the top is important
10 also for the short term exposure risks that we want to
11 evaluate for particular workers. So if we can move to
12 the next slide please.

13 So if you think about it, RWW representing
14 various values in terms of within worker correlation
15 relative to the total variation, their average within
16 variation to the total variation. We can sort of
17 understand how we can progress from this single
18 exposure down to a long term exposure. And what we're
19 looking at here is what would be the progression and
20 how might it go depending on where RW is.

21 If you have a large within worker
22 correlation, remember that means within worker
23 variation is very small, then we're going to have a
24 distribution that's going to be fairly spread out
25 because these individuals are going to have their means

1 spread out all along this line. However as you start
2 increasing that RWW, in other words the variability,
3 excuse me, as you start decreasing the RWW, that within
4 worker variability is going to be increasing and
5 becoming more similar to the single day distribution
6 for all the individuals. And their averages, because
7 they're spread out across this whole line are going to
8 start to move in towards this arithmetic mean which
9 we've highlighted going all the way down through here.
10 So the distribution in point of fact will actually
11 begin to get tighter and tighter.

12 If RWW is zero then essentially your long
13 term distribution is going to end up being equivalent
14 to the arithmetic mean. Obviously this is probably not
15 the case, nor is it a case where it's essentially up
16 here, it's somewhere in between. But all these
17 distributions as we see here have the same particular
18 mean exposure. Next slide please.

19 So what this means, by knowing this within
20 worker correlation we can take and predict from our
21 single day exposures or our single exposures for the
22 between worker distributions, using this within worker
23 correlation and come down to an estimation of the long
24 term mean exposure for the between workers. And in
25 many cases this is really what we're interest in

1 getting at. Next slide.

2 So the question is, how do we go about
3 estimating this within worker correlation? There have
4 been some studies and some literature done and which my
5 colleague, Doctor Holden, has gone back and looked at
6 these particular studies and used the data from these
7 in the analysis that was done on these studies to try
8 and develop estimations of this within worker
9 correlation. And there's one case here with Doctor
10 Fromanegerol, there were only 2 air blast applicators
11 and 2 open pour mixer/loaders, there were repeated
12 measures over 6 weeks.

13 The issues that we have with a study like
14 this is that it tends to underestimate the total
15 scenario variability and it also tends to underestimate
16 as a result, the within worker correlation. We have a
17 limited number of workers and a limited number of
18 applications.

19 These other studies her, there has been a
20 more or less meta-analysis to try and come up with the
21 within worker correlation as well, I'm sure Larry will
22 correct me if I get this wrong. These are measured
23 actually quite close together as well and they have a
24 tendency to be done under similar conditions which
25 tends to underestimate the long term within worker

1 variation and overestimate the correlation. Again we
2 also have one other example here where we have some
3 purchased data that the AHETF went through. It was
4 repeated measures, exposures but they were 1 to 6 days
5 apart, very limited in terms of the variability that
6 you might expect to see within an individual worker.
7 And this is going to be an issue with trying to do any
8 kind of an estimation of this is that you're going to
9 have these sorts of problems cropping up in these
10 different studies. What basically these, examination
11 of these studies indicated in the literature was that
12 this within worker correlation is probably between the
13 range of .2 to .5. So if we can go to the next slide
14 please.

15 So what if we wanted to go ahead and actually
16 get a better estimate of this within worker correlation
17 in the program? Again, we're going to start out with
18 our single day exposure, and again you're going to have
19 these different workers that will have this type of
20 variability on. We need to collect this data.
21 Regardless of anything else this has to be collected
22 because we need to address the short term as well as
23 the long term exposure.

24 With that emphasis in mind that's why the
25 AEHTF is focused on this particular box in its design

1 at this point in time. If we start looking at trying
2 to get multiple monitoring units with the same worker,
3 and as Larry pointed out earlier, when we talk about
4 the worker they're not necessarily having all the same
5 conditions relative to their application of a pesticide
6 to the field. They are not the only component that is
7 being varied from one monitoring unit to another.

8 It could be a change in equipment, it could
9 be a change in the acreage, it could be a number of
10 things that change. So it's not strictly speaking just
11 a worker effect that you would measure. What this
12 would tend to do is obviously you're going to have to
13 at least double the number of required monitoring units
14 to get any kind of an estimation on this within worker
15 correlation.

16 If you start going to more than that then you
17 start running into obviously more monitoring units.
18 All of these things tend to create some logistical
19 issues, participation, personnel issues, equipment,
20 analytical issues, how far apart is far enough apart,
21 if we do everybody within a couple days is that giving
22 us enough estimate of the within worker exposure, do we
23 need to do it over months, do we need to do it over
24 years? If we have to do it over years we start running
25 into some major logistical issues just trying to

1 execute the study. Next slide please.

2 To try and really get a feel for where this
3 is going Doctor Holden did some simulation runs to see
4 how this might be impacted. Using a geometric standard
5 deviation of 4 and 25 workers, there were some
6 simulations done in which a between worker component of
7 the variation was estimated and then a subset of that
8 added to it was within worker variability.

9 So you start out with 25 workers and if you
10 have to do 2 reps per worker obviously you're up to 50
11 monitoring units to begin with now and what kind of an
12 impact would it have if our true within worker
13 correlation is .3? And the simulation was set up with
14 this correlation being the actual within worker
15 correlation in the simulation.

16 So you can see here it ranges from roughly
17 zero to about .61, call it .6. If we go to three
18 replicates per individual we're now having 75
19 monitoring units and we've gotten a slight improvement
20 on the top end, the bottom end is still essentially
21 going down to zero, we're slightly above 5, maybe 5.3.
22 If we have 5 replications per worker we're now up to
23 125 monitoring units and so forth.

24 If we go down to the last line here we're up
25 to 250 monitoring units for the single study with 10

1 replicates per worker. And what we have succeeded in
2 doing is moving the bar from zero to about .15 call it
3 to about .43. And relative to what we've seen in the
4 literature that was .2 to .5 based on the literature
5 data that we have at this point in time. So as you can
6 see what we're seeing in this simulation is that we're
7 going to have to have a substantial increase in the
8 number of monitoring units to get a true benefit in
9 trying to narrow down the estimate of the within worker
10 correlation. Next slide please.

11 So in summary what we have at this point in
12 time is that the existing data suggests that the within
13 worker correlation is .2 to .5, there appears to be a
14 large increase in samples that would be required to get
15 a meaningful tightening on these limits. In other
16 words we're going to have to substantially increase the
17 number of monitoring units to get any kind of a
18 substantial decrease in that range.

19 We do already have within place an existing
20 process to address long term exposure risk. Using the
21 between worker distribution of single exposures and
22 reasonable assumptions about this within worker
23 correlation we can already move in that direction. And
24 it's important to keep in mind that the between worker
25 distribution, that initial box I kept on pointing to at

1 the top, will be needed for both short term and long
2 term exposure assessments. Thus it's of the greatest
3 regulatory importance as far as we can tell.

4 With that in mind our basic conclusion that
5 is attempting to measure the within worker correlation
6 in the monitoring program would have a tendency to
7 waste the resources and lead to unnecessary human
8 testing. For that reason we're advocating moving away
9 from doing multiple repeated, excuse me, multiple
10 monitoring units on the same worker and instead trying
11 to maximize the number of workers that we actually
12 measure in the monitoring units. Thank you.

13 DR. HEERINGA: Questions from the panel?
14 I have one but I'll hold it and wait until Dallas asks
15 it for me. Ken, Doctor Portier.

16 DR. PORTIER: Could you go back to slide
17 7. So if I understand this the top distribution is
18 your distribution of between worker, that's your
19 between worker distribution, right? So an individual
20 worker drawn at random would have a value from that
21 distribution which would represent their long term
22 exposure if we repeated them over time a lot, right?

23 DR. LANDENBERGER: That's correct.

24 DR. PORTIER: Okay, good. Now, if I
25 assume say a large actually, shouldn't it go the

1 other way around? If you assume large within worker
2 correlation or you assume the second distribution is
3 that worker's repeated measures distribution, okay,
4 what would happen is that distribution really is
5 shifted to the mean of the value you chose at the top,
6 right? So if I had a worker who was at or near the
7 protective level in their average exposure, when I
8 overlay on that the repeated measures distribution and
9 I start worrying about how often is this worker going
10 to be above some threshold exposure level, it's very
11 important whether I have large worker correlation or
12 small worker correlation.

13 DR. LANDENBERGER: Let me just clarify,
14 I'm not sure I heard you correctly. You were saying
15 large within worker correlation or large within worker
16 variation, because that was --

17 DR. PORTIER: Well I really mean, I'm
18 looking at large within worker variation, I'm looking
19 at that second distribution so that's an individual
20 with a lot of variation, right

21 DR. LANDENBERGER: Yes.

22 DR. PORTIER: versus the bottom of the

23 DR. HOLDEN: No, no, that's wrong, it's
24 just the opposite, the largest variation of within
25 worker is actually the bottom.

1 DR. LANDENBERGER: And what you would have
2 here is if you look at this distribution representing
3 everything your various measurements on that individual
4 are going to be here.

5 So what's going to happen, there's actually a
6 slide we took out which we probably should have left
7 it, that their averages are going to tend to start to
8 come in towards this arithmetic mean because you'll
9 have, they'll have some high values, you're correct,
10 they'll also have some low values. Now if they're out
11 here in terms of the distribution towards the upper end
12 of the tail and they had tight within worker variation,
13 you're correct that they would probably not move much
14 from that point but it is, you know, questionable about
15 where they are relative to this.

16 But the other issue is too that that is,
17 they're probably not going to move too far so if
18 they're initially out here, yeah, that's an issue. If
19 they're here it may not be an issue depending on how
20 tight that within worker correlation is. If it's
21 widespread then we would expect them to have values all
22 along here and that mean is going to tend to move in
23 towards this arithmetic mean in the middle.

24 DR. PORTIER: The point I was trying to
25 make from a regulatory setting, if the workers are very

1 consistent in their exposure then you have to worry
2 about which workers are exceeding that threshold. If
3 the workers are very variable in their exposure then
4 every worker has a chance of exceeding that threshold
5 and it's a different kind of risk scenario. That was
6 the point I was trying to make. And it ties in with
7 how we look at this within worker variability, within
8 worker correlation issue.

9 DR. LANDENBERGER: I'm going to say I both
10 agree and disagree. In terms of it being critical and
11 important for understanding a risk assessment mode I
12 would agree. It doesn't change where the distribution
13 goes.

14 What would be impacted by that is where you
15 set this critical red value here, I'm putting on my
16 risk assessment hat, in terms of protecting those
17 workers. Because that's the issue of protection for
18 the worker. You're never going to guarantee that you
19 protect every worker and if we had a distribution that
20 was really tight at this top end, yes, that would be an
21 issue that needs to be addressed.

22 But in terms of the within worker variation,
23 I think based on what we have already within the
24 literature, we can sort of develop what that long term
25 exposure would be. Long term I expect people to move

1 to the arithmetic average because they're going to have
2 some days when they have high exposure and some that
3 they have low. But the combination of those are going
4 to bring them in towards the center. If you're looking
5 at short term exposures you're going to want to use the
6 top distribution between worker anyway and that'll get
7 you to the point where you're wanting to look at what
8 the upper end of the protective level is.

9 DR. HOLDEN: Doctor Portier, I don't
10 disagree with that. I was just going to say is that,
11 and I may be misunderstanding as well but what we're
12 really saying is that, what you were talking is very
13 important, is absolutely correct I think and that
14 variation is important, but I think what I pointed out
15 in this discussion here is that we can infer some
16 things with reasonable assumptions about the within
17 worker unit measure of distribution from data that
18 would almost be counterproductive in trying to collect
19 for this generic database and I think that's really the
20 point.

21 Not that the information is within worker
22 variation is unimportant. Actually we think it is
23 important but just that we don't think that we can,
24 with the data that, with the resources that we have, we
25 could do it justice, do it even better than just

1 reasonable assumptions.

2 DR. PORTIER: And I follow that, I mean I
3 follow that logic, I'm just trying to, you know, it's
4 one thing to say, we don't think it's important and
5 another thing to think through that issue and say, you
6 know, well, under what conditions might it really be
7 important?

8 And that's what I'm trying to take the
9 opposite side and argue. From the industry point of
10 view I follow your argument perfectly. But now from
11 the EPA's point of view is that really where they want
12 to go? If they have any say in this is that the best
13 thing for them, thinking about all the scenarios that
14 they have to face which is not just tier 1 and tier 2,
15 they also have other environments where this data may
16 be very useful.

17 MR. LUNCHICK: Let me address that on
18 behalf of the industry. I don't want to speak for the
19 Agency and I think if they want to add something it
20 would be beneficial for them to come up.

21 But I'm going to present this from a non-
22 statistical standpoint because I got lost about 15
23 minutes ago, but what I, when I assess exposure, and
24 let's take this distribution, yeah, I was just thinking
25 of that for you, we're assuming, and I think our

1 experience shows and what Bryce showed is we have a
2 decent amount of intra-worker variability so at any
3 give time an individual is going to be scattered along
4 this. But if I am looking at one of my products and
5 there is a risk concern out here, regardless of whether
6 I can do any statistical tests, Larry keeps telling me
7 I'll never be able to do a statistical test that's
8 significant, but I would use my experience, we are
9 collecting a huge amount of information when we do our
10 studies.

11 I would start to look at what conditions are
12 going on here. And let's say it's tank loads or
13 something like that or it's some type of worker
14 property or it could even, you know, whatever, I would
15 begin to focus on that.

16 I can guarantee you because I'll be working
17 with EPA or DPR or PMRA, we will begin to focus on what
18 conditions may be occurring here that are of concern
19 and not on a task force basis, but on a registrant to
20 regulator basis, we would begin to see if we need more
21 information to delineate something important here that
22 would allow us to hopefully mitigate exposure because
23 the alternative is something a registrant generally
24 doesn't want which is the Agency is going to prohibit
25 any use that would occur beyond this level of concern.

1 DR. HEERINGA: Cynthia Hines.

2 DR. HINES: Just a comment on the last
3 slide and it's just a comment on language. I think
4 obviously collecting repeated measurements, and I know
5 from personal experience in an agricultural setting is
6 very sobering and very challenging because of the short
7 time windows you're working with and the applicators
8 may only do a few applications, if that, within a year.
9 So I acknowledge just how difficult that really is.

10 I would comment though that I don't think a
11 reason to not do it is unnecessary human testing, I
12 think that's, it may be unfortunate language, because
13 if you are looking at the natural variability within
14 workers you're actually trying to capture that
15 variability from day to day or week to week or month to
16 month under their normal conditions or what they're
17 usually doing that you aren't actually manipulating or
18 scripting what they're doing. And so is that just
19 unfortunate language?

20 DR. LANDENBERGER: Yeah, I think that's a
21 fair comment.

22 DR. HEERINGA: Good for you, Dallas.

23 DR. JOHNSON: Yeah, just to play the
24 devil's advocate here a little bit, have you thought
25 about this interclass correlation with respect to

1 studies and workers within study?

2 DR. HOLDEN: Yeah, actually I have but,
3 and not only that but you can imagine, the other day
4 you were talking about clustering, we'll talk about
5 that later being temporal as well as spatial if you
6 think about an individual. And we have looked at some
7 of these various components just to see what impacts it
8 has and if you look at it over long periods of time,
9 you know, there's temporal correlation.

10 With an individual you'd expect that. In
11 other words his or her value you get tomorrow is more
12 likely because of the value today than it would be say
13 three years from now because there are many ways. So
14 you could model that normally in a simplistic way by
15 thinking there's a spatial cluster and also a temporal
16 cluster.

17 But now when you're talking, but if you
18 forget that and just talk about spatial and within
19 worker correlation, a worker is almost always going to
20 be within the same cluster over repeated times. Until
21 you get long period of times you're going to be in the
22 same, what we're calling a sampling cluster. So that
23 means that the within worker correlation can't be any
24 smaller than the within cluster correlation. It has to
25 be at least that.

1 And maybe bigger. And so there are some,
2 there's a relationship between this what I'm calling
3 clusters which is just a sampling artifact and I'm
4 visualizing it to model it. And so there are some
5 relationships that have that in there and since it
6 looks like our, a few of our scenarios are in our
7 cluster correlation is around .3, that sort of suggests
8 that the within worker correlation has to be at least
9 that.

10 So it may be more like .3 to .5 or maybe .6
11 or something like that. So if you pick some sort of
12 number in the middle that's probably close to what it
13 might be given those kinds of, you know, that logic if
14 you want to call it logic, gut feel, seat of the pants,
15 whatever it is you want to call it.

16 And of course we sort of inferred this but we
17 didn't really say this that an agency, the EPA or some
18 other regulatory agency, if they chose could pick zero
19 or 1 depending on which is more conservative for their
20 needs to protect, I mean that's the extreme, right?
21 The extreme would be to pick a correlation of, assume a
22 correlation of 1 and then they would always use the
23 between worker distribution for everything which would
24 be super protective in a sense for chronic exposure.
25 So some reasonable assumptions could be made to handle

1 some of these things.

2 DR. HEERINGA: David Miller from the
3 Health Effects Division.

4 MR. MILLER: I'll probably just, I may
5 just end up repeating some of the concepts, but I'll
6 add a few others. If we could just go back to the
7 slide with the four graphs, distributions. Yeah,
8 great.

9 Basically, I mean if the top one for example
10 and again, this has already come up but I'll just say
11 it, that's the between worker distribution for single,
12 single days and the question that's kind of come up at
13 the Agency and we're talking about is, in essence when
14 we, it's the sloppy versus neat aspect, when you
15 repeat, when you, a worker, this is just for a single
16 day one, when you go out and do it a number of
17 different says, the same worker, if they're
18 consistently sloppy at the upper end they'll
19 essentially remain at the upper end and if they're
20 consistently neat, if they're at the lower end they'll
21 remain at the lower end.

22 And the worry is, and just to give an example
23 in terms of one of the things that's of interest is,
24 potentially why are they at the upper end and why are
25 they consistently at the upper end? A lot of it may be

1 due to behavioral practices for example. I just, off
2 the top of my head it might be instead of if you're
3 doing a backpack spraying for example instead of
4 walking backward for example as you spray, if you walk
5 forward and that's your habit you would consistently be
6 at the upper end.

7 So that's kind of the interest in terms of us
8 in terms of why we think the interclass, the worker
9 variation consistency is important.

10 Currently what we do is when we look at, we
11 have the, we don't look at the intra within worker
12 variation. Essentially we just use the average is what
13 it is. So there's, it's as if everybody is randomly
14 bouncing around from high end, from the top
15 distribution to the lower end of it or so. So there's
16 no consistency, necessarily consistency within workers
17 in their exposures.

18 So the question that we're I guess addressing
19 here is, how important is that for example and how much
20 needs to be done in order to kind of clarify some of
21 that? And I think that what the Task Force is bringing
22 up is you would have to do an awful lot of replicates,
23 true replicates within workers in order to get a better
24 idea of that and it may be just the, from the
25 literature .2 to .5 may be sufficient.

1 And as I think at the tail end it may be just
2 you can do the extremes of those for example and end up
3 with something that's good information, that's better
4 than what we have now.

5 DR. HEERINGA: Thank you very much Mr.
6 Miller. Steve Heeringa here. This is something I know
7 a little bit about and I think that as I look at what
8 the discussion, the factors that you just mentioned,
9 David, with regard to trying to understand which
10 individuals in the population may be at higher risk or
11 essentially their expected value is up at the tail of
12 that distribution, the factors you pointed to weren't
13 really the individual factors, they were fixed effects
14 of their working conditions, backpacks, wind velocity,
15 type of volume, et cetera.

16 So those really aren't individual, you know,
17 these measures would really be pure random effects and
18 in a sense you would be better off I'll hold my
19 comments later on but the short of it is that if you
20 want to describe the population distribution of an
21 attribute like unit exposure you wouldn't cluster or
22 multiply measure anyone if there's a positive
23 correlation.

24 You're just losing statistical information
25 and if we go back to slide 11 these arrow bars, I mean

1 most of us could calculate. The difference between
2 these obviously is they grow narrow and that's because
3 you're increasing sample size. And I suspect it's not
4 quite a square root function going from A to B to C to
5 D because there is some design affect inefficiency due
6 to the interclass correlation and the cluster size.
7 There's a little simple formula for means that operates
8 there.

9 But, you know, the picture here, we shouldn't
10 be misled, the reason this picture is changing is
11 because we are adding those observations and the
12 picture would change even more sharply if we, instead
13 of repeated measures, just took 250 observations on
14 independent individuals doing independent things. And
15 that'll sharpen it up.

16 So I think you've got a critical point here
17 and that is that whether you do repeated measures on
18 individuals that will benefit a certain type of intra-
19 individual analysis if you were really interested in
20 these components of variance.

21 But with 15 observations on a scenario and
22 multiple scenarios and many other factors compounded
23 with the individual repeated measurements, you will not
24 be able to tease that out. I'll say that again this
25 afternoon.

1 Yes, Doctor Johnson.

2 DR. JOHNSON: Yeah, while we're on that
3 particular slide I just wanted to say that you could
4 probably change those arrow bars on RWW a lot faster
5 for the total number of monitoring units if you were to
6 increase the number of workers. So there's two ways to
7 get to the 250, one is to keep it at 25 workers and
8 look at 10 reps per worker but another way would be to
9 have 125 workers and two observations per worker. And
10 you would get a lot narrower bars I think on that true
11 interclass correlation.

12 So you're looking at the between variability
13 over the total and it's the between variability that
14 you're not measuring very well because you only have 25
15 workers or 24 degrees of freedom associated with that
16 and you've got lots of degrees of freedom associated
17 with the within worker part.

18 DR. HEERINGA: Doctor Holden.

19 DR. HOLDEN: Actually that's correct, I
20 mean, yeah, that's true, you can, it's the, it's the
21 combination of both of them. But there is some sort of
22 a tradeoff because we're talking about estimating the
23 correlation, not estimating the mean or something like
24 that.

25 But nevertheless you're right, the general

1 picture is the same is that it's the total resources.
2 I don't know what the exact balance is, I imagine that
3 there is some, one's going to be more efficient than
4 the other. Certainly for measuring, if one wanted to
5 do both you'd put more information into more workers
6 than you would into repeated measures.

7 But then I probably would want to, almost
8 insist in that case that you separate these workers by
9 a bit more longer in time than you might, you know, I
10 think some of these studies where you measure a worker
11 in the morning and then you do him again in the
12 afternoon or the next day, you're probably
13 underestimate or overestimating the correlation,
14 underestimating the variability. That might be more
15 relevant.

16 DR. HEERINGA: Thank you very much. A
17 clarification on my comments too. I was looking at
18 this as arrow bars on mean. This same affect would be
19 observed, that's a good point. This is essentially
20 arrow bars on the estimated interclass correlation.

21 DR. LANDENBERGER: Just one clarification
22 on these bars, these are actually empirical ranges from
23 a simulation, 10,000 runs on each one of these.

24 DR. HEERINGA: Very good. Other questions
25 on this presentation? Okay, am I correct that we have

1 one more presentation this morning in this group?

2 DR. LANDENBERGER: We're done.

3 DR. HEERINGA: We're done, okay. What I'd
4 like to do then is to move on to at least an initial
5 discussion of the question, charge question number 4.
6 But before I do that I indicated to the panel members
7 and to the participants here that I would allow
8 individuals an opportunity at the start of each day's
9 charge question session to go back to add additional
10 comments on prior charge questions that had been
11 covered.

12 Is there anything for the panel members that
13 has been presented or discussed here this morning or
14 any thoughts that you've had over the past sixteen or
15 so hours that would cause you to modify or amend any of
16 your comments or extend your comments from yesterday on
17 any of the charge questions? And if so if you would,
18 when you speak just say, this is in relation to charge
19 question x and I have this comment. Any members of the
20 panel? Doctor Popendorf.

21 DR. POPENDORF: Yes, I was just trying to
22 think back on the question but as Mr. Evans points out
23 this morning I commented yesterday with regard to
24 biomonitoring, simultaneous biomonitoring and passive
25 dosimetry, I didn't recommend that but there was a

1 misunderstanding in terms of the goal of the
2 biomonitoring.

3 So I would amend what I said in that regard.
4 And I thought a little bit about that and I can see
5 some benefit to doing the biomonitoring as a, if you're
6 doing a good job of passive dosimetry your
7 biomonitoring would essentially be zero. And if you
8 get any detects then you would be able to get some
9 estimate of breakthrough or inefficiency of your
10 passive dosimetry.

11 On the other hand I think I wouldn't
12 recommend it be a requirement because the practical
13 aspects of being able to find someone with no prior
14 exposure and probably no subsequent exposure without
15 the passive dosimetry would, any biomonitoring would be
16 for that particular day.

17 That would be a big restriction on trying to
18 collect data. If it works it's a good backup but it, I
19 couldn't see it being a requirement, I wouldn't
20 recommend that. It would just make it very difficult
21 to get representative users.

22 DR. HEERINGA: Thank you very much Doctor
23 Pependorf. Other members of the panel? Doctor Barr,
24 are you okay, it looks like Jeff is going to leave
25 the building so I won't ask him to read the charge

1 question so I'll tell you what, Doctor Portier has a
2 good suggestion, it's 25 to 12:00, let's take an early
3 lunch and if we could have everyone back here at 12:45,
4 let's do that.

5 And I think that makes sense and then we'll
6 start on charge question 4, we'll be 15 minutes ahead
7 of where we need to be in the agenda.

8 Just a little foresight for those of you who
9 I know are making travel plans for tomorrow and many
10 people in the audience, I do not believe that we will
11 try to accelerate things to finish today, there's just
12 no way to do that.

13 The agenda is sort of set with an
14 interspersion of presentations and questions. I do not
15 anticipate to go overtime on tomorrow's session by any
16 means but I think we need to maintain the agenda
17 roughly as it is.

18 And I think the chances of us ending early
19 today or finishing up today with the public part of the
20 meeting or the general meeting of the SAP are small.
21 So we'll stay with the general agenda so would expect
22 to be here again tomorrow morning for those of you.

23 But I do expect to be finished by the time
24 that we are scheduled to be finished at noon.

25 (WHEREUPON, the meeting was adjourned for lunch.)

FIFRA SCIENTIFIC ADVISORY PANEL (SAP)
REVIEW OF WORKER EXPOSURE ASSESSMENT METHODS

January 11, 2007

Afternoon Session

DR. HEERINGA: Welcome back everyone to the afternoon session of the third day of our four day meeting of the FIFRA Science Advisory Panel meeting on the topic of a review of Worker Exposure Assessment Methods.

This morning we heard several presentations on statistical aspects of the problem of exposure measurement and also on the design of the Agricultural Handlers Exposure Task Force AHED program, sort of motivations and design considerations for that.

At this point in the agenda we have, we're going to return to charge questions to the panel. And before we begin I guess I'd like to offer one more opportunity for panel members. Is there anything you would like to revisit on questions number 1 and 3 at this point?

Not seeing anything then I guess, Mr. Miller if, or Matthew if you would want to read the charge question number 4 into the record please.

MR. CROWLEY: This is Matthew Crowley, Health Effects Division, EPA.

1 The normalization of exposure by amount of
2 active ingredient handled, the unit exposure has since
3 the mid-1980s been a principle of the relationship
4 underlying the use of exposure data in the Agency's
5 pesticide handler exposure assessments. It is based on
6 the assumption that the two variables are proportional.
7 That is, if one doubles the amount of pesticide they
8 handled or applied the resultant exposure will be
9 doubled as well.

10 The Agency is unsure whether the results of
11 our exploratory work showing that proportionality
12 between exposure and amount of active ingredient
13 handled is reasonable in some, but not all cases as a
14 function of the limitations of the data within PHED or
15 whether this relationship is in fact not a reasonable
16 assumption for all scenarios.

17 It may be the case that an additional
18 ancillary variable, for example, boom length, number of
19 tank mixes or number of decouplings in a closed loading
20 system in addition to or in place of the amount of
21 active handled may improve the predictive capabilities
22 of our exposure model.

23 Though it is recognized that neither the
24 studies in our current database nor the proposed
25 studies by the Agricultural Handlers Exposure Task

1 Force were designed for the primary purpose of
2 examining proportionality between exposure and amount
3 of active ingredient handled, or to determine the
4 extent to which other parameters influence exposure
5 compared with our current database.

6 The Agency believes that the proposed AHETF
7 studies will generate data that will reinforce the
8 assumption of proportionality between exposure and
9 amount of active ingredient handled, or alternatively
10 inform the applicability of another variable as a more
11 appropriate predictor of exposure.

12 Based on the themes presented on this topic,
13 including its historical precedent, it's application in
14 risk assessment and subsequent risk management
15 decisions, the Agency's exploratory work using the six
16 PHED scenarios in the case study and the study design
17 and objectives of the AHETF, please comment on the
18 assumption of proportionality between exposure and
19 amount of active ingredient handled as a default.

20 Also, please provide comments on whether the
21 proposed AHETF study design is adequate to evaluate
22 proportionality between exposure and amount of active
23 ingredient handled. What other parameters should AHETF
24 study designs measure in order to improve the
25 prediction capabilities of our exposure model?

1 DR. HEERINGA: Thank you very much.
2 Doctor Lu is the lead discussant of this particular
3 question. Alex.

4 DR. LU: Good afternoon. I think this
5 question can be answered in a different direction. I
6 think the panel with their different background
7 expertise, I'm sure they're going to attribute it from
8 their perspective as well.

9 I'm going to look at this from just from the
10 exposure assessment perspective and pharmacokinetics.
11 I think in theory absorbed dose increases
12 proportionally with the exposures. In these
13 discussions the matter is whether the Agency is using
14 the right or statistically significant surrogate for
15 dose and exposure respectively, or the Agency is simply
16 just trying to extend its exposure and dose paradigm to
17 add another component which is the amount of active
18 ingredient handled before the exposure term.

19 So if I can show the data, I just, it just
20 kind of struck me this morning that I do have some data
21 that can kind of validate this statement here. If I
22 can have the pointer.

23 Anyway, look at this graph, this is animal
24 data, it's a controlled dosing animal data, this is for
25 Atrazine and this is published data so I feel

1 comfortable presenting it here.

2 Look at this, I'm sorry, I should point to
3 there. Look at this black square. It represents the
4 how come the figure, the legend is not showing, anyway,
5 this is the plasma concentration of the Atrazine that
6 are dosed to the rats. And those are the saliva
7 concentrations. Okay, so look at, this is one
8 milligram per kilogram of Atrazine and this is 10.
9 Okay, as the dose increases the exposure increases or
10 vice versa. So that's very clear. Again this is an
11 animal controlled study it may not be applicable to the
12 field of human data. But again in theory this
13 proportionality exists. Next slide please.

14 Okay, do you want to scroll it down a little
15 bit. Okay, again this is animal data, this is for
16 Diazinon, they're similar studies. Again this is the
17 plasma concentration, you can ignore the saliva, it's
18 for different purposes. The concentration was obtained
19 from the 10 microgram, no, I'm sorry, 10 milligram per
20 kilogram of dosage. Scroll down a little bit. So the
21 highest concentration is somewhere around 800 ppb.
22 Going down, going down. So the next graph shows
23 essentially the similar data except the high, the peak
24 concentration is somewhere around 100 which reflects
25 the lower dose that were given to the rats which is 1

1 milligram per kilogram. So this data, and those are
2 all published data, okay? The reason I want to show
3 those data is to just kind of prove in theory this
4 proportionality exists.

5 The question is that, what is your definition
6 of exposure? What is your definition of dose? Or
7 simply you just want to create another component in
8 front of exposure. So here is the amount of active
9 ingredient handled. Here is exposures, here is the
10 dose. And you try to validate these two boxes the same
11 way that, you know, that is shown between exposure and
12 the dose.

13 The study that was presented by the Task
14 Force provided actually a more realistic approach to
15 assess these problems, these issues. Besides the
16 exposures and other factors, many amount of active
17 ingredients handled, they're not known or can be
18 quantitatively or qualitatively assessment. A random
19 variable, the term that is added to the algorithms and
20 which may or may not affect the exposures. However,
21 according to the presentation made by the Agency using
22 the PHED data, this random variable may likely not only
23 exist, but affect the result, the resulting exposure
24 substantially as well.

25 This is evident by the PHED case study

1 scenario number 2 in which the relationship between the
2 exposures and the amount of active ingredient handled
3 is dramatically different in terms of the slope of the
4 linear line, 2.1 versus -0.26 although the tasks of
5 this application is the same which is the open loading
6 granule. So in these two cases the random variables
7 that are proposed by the Tash Force study actually
8 affect the results substantially. So one of the charge
9 questions is that, do we need to add another term or
10 look at other factors that affect, may affect this
11 proportionality. I think that's probably a wise
12 approach.

13 The Agency made a presentation about their
14 future efforts in facing in this the desire of
15 investigating the proportionality between exposure and
16 the amount of active ingredient handled. In the future
17 studies it's absolutely needed however, if the
18 objective of doing this exercise is to use the data in
19 the risk assessment paradigms then the agencies as well
20 as the task force group should actually incorporate the
21 absorbed dose into the whole exercise as well.
22 Because, for example if you end up, if you can validate
23 this proportionality by adding new data or whatever you
24 want to do, the next step is to incorporate this
25 exposure to the risk assessment and you're going to

1 transfer the metrics from the exposure to dose and
2 there's another black box that you have to work on.
3 And so instead of doing it later you might want to do
4 it now.

5 Assuming the proportionality between exposure
6 and the amount of active ingredient handled is proven
7 valid for any reason, the same proportionality should
8 also be proven valid before it can be used in the risk
9 assessment, meaning exposure and the dose. So the task
10 force people propose that at the end they're going to
11 normalize the exposure with the active ingredient
12 handled to come up with the best estimate in terms of
13 this proportionality. I thought that might be, that
14 might not be the right approach. What should be done
15 is that using the amount of active ingredient handled
16 as a modifying factor. For example, in the morning
17 discussion there was a phrase that came out that the
18 sloppy people tend to be sloppier and that's why they
19 get higher exposures.

20 So, think about this scenario, if the person
21 is really sloppy, the more the pesticide this person
22 applied the high exposure will likely happen to this
23 worker. But if you normalize the amount of active
24 ingredient handled you dilute the affect, the true
25 affect that this sloppy guy actually has a very high

1 exposure.

2 On the other hand if a person as a pesticide
3 applicator is very careful, follows all the standards,
4 guidelines and the labels, so no matter how much
5 pesticide that he handled or applied, his exposure will
6 still be very low.

7 So this modifying factor will not affect the
8 final exposure and probably not the dose as well. So I
9 would not say you should normalize, that you should use
10 this amount of exposure as a controlling factor,
11 modifying factor that would kind of compensate for good
12 reasons as well as for bad reasons.

13 That's all I have for this question.

14 DR. HEERINGA: Doctor Appleton is our
15 first associate discussant on this question.

16 DR. APPLETON: Thank you. Well since this
17 is totally out of my field for a change and I couldn't
18 steer everything back to biomonitoring, I guess we got
19 close here, I'll be the one that says the nice things.

20 I'd like to commend both the EPA and the
21 industry task forces for all of their work and more
22 rigorously defining or trying to explain the potential
23 sources of variability that we see in the measurement
24 of one of the key assumptions, that is the
25 proportionality of exposure with the amount of active

1 ingredient handled. This is a key assumption that was
2 accepted without much debate 25 years ago at the EPA, I
3 was a fledgling scientist in the exposure group back
4 then, but kind of sat as a fly on the wall watching it
5 all happen.

6 And I accepted along with most other folks
7 that there was a proportionality in the relationship,
8 it's very intuitive and you can find examples in other
9 kinetic examples as we just heard to support that. And
10 to a small extent my branch chief suggested that I did
11 accept that notion.

12 I'm not sure where all of this discussion
13 will lead in terms of being a user of either the
14 Pesticide Handler Database or the Agricultural Task
15 Force's database, so until I hear differently I suppose
16 I will operate business as usual and assume
17 proportionality.

18 My only real tangible recommendation I can
19 make on this right now is that as a PHED user for the
20 Forest Service I would really strongly and somewhat
21 selfishly recommend that EPA not give up on the PHED.
22 Stick with it and do try to find out as much as you can
23 with the resources that you have to use the data. And
24 I say that not only for my organization but for many
25 other organizations that deal extensively with more

1 minor use pesticide issues that may or may not be
2 addressed by the agricultural database. We grow tress,
3 we don't grow, you know, a country full of winter
4 wheat, so things of that nature, understanding that the
5 industry has its own agricultural regulatory needs. So
6 those are really the only comments I have so I'll rest
7 with that.

8 DR. HEERINGA: Thank you Doctor Appleton.
9 Paul Hamey, doctor Hamey.

10 DR. HAMEY: Thank you. I think just sort
11 of thinking about the issue in advance of looking at
12 the data I think we can sort of hypothesize that for
13 example where exposure arises through contact with
14 airborne material evolved at a fairly uniform rate,
15 there might be sort of a strong association between
16 amount handled and applied. And we might find this for
17 example when measuring exposure during the handling and
18 applying granules where airborne dust is generated
19 during hopper filling. And I've seen at least one
20 modern regulatory study where there was quite a nice
21 relationship between the amount of exposure and the
22 amount of granules handled.

23 And so I think, you know, under some
24 circumstances we can imagine there will be a
25 proportional relationship.

1 But as already suggested this morning I think
2 we can also imagine alternative situations where
3 exposure results mainly through contact with
4 contaminated surfaces and where the residues on such
5 surfaces may be at a equilibrium plateau or a sort of
6 constant level. And for example with mechanical
7 transfer devices for loading liquids were mentioned and
8 here the exposure is probably limited to contacting the
9 concentrated residue left on the dry break coupling
10 which is actually independent of the amount
11 transferred. It is affected by the concentration of
12 the active ingredient in formulation so even in that
13 situation under some circumstances you might find some
14 relationship.

15 Other sort of situations where the user is
16 protected in a closed cab when making ground boom
17 applications, an exposure might occur there when
18 handling the contaminated boom or nozzles and the
19 outside of the cab and particularly residues on the
20 doorhandle of the machine.

21 So exposure could, in those two scenarios be
22 proportional to the number of decouplings or the number
23 of times the driver leaves and reenters the cab, both
24 of which may not be directly related to the amounts or
25 indeed any other useful parameter that we can

1 determine.

2 So for some scenarios we may not, well I do
3 not expect a strong relationship will be found.
4 However I think the assumption probably serves as a
5 reasonable default but I would caution that this may be
6 true within a closely defined scenario but may be more
7 challenged when we have wide scenarios of work tasks
8 and practices and equipment within those scenarios.

9 For example if we consider ground boom
10 sprayers these may range from small antique machines
11 mentioned yesterday to state of the art large modern
12 self-propelled machines with induction bowls, clean
13 water supplies for washing gloves before removal, glove
14 lockers to put your gloves in after you've taken them
15 off before you get in the cab, automatic folding booms
16 and with the operator and the equipment controls
17 positioned in closed air conditioned cabs. Such
18 machines, the latter machines will achieve much higher
19 work rates and consequently the user will handle more
20 pesticide but because of the technical controls the
21 unit exposures will be much lower than on the old
22 antique machines. And if we have all the ground boom
23 machines in one category then we're misleading
24 ourselves.

25 I think it's also reasonable to consider the

1 data used to derive the specific unit exposures in more
2 detail. And if the unit exposures are derived from the
3 antique machines then we would expect the unit exposure
4 to be overprotective in the case of modern equipment,
5 but if it's the other way around and the data would
6 derive with the modern equipment then we may
7 underestimate what's happening with the antique
8 machines. So that's two additional points to consider.

9 And I think I've also got some brief comments
10 to make on the figures presented in the EPA's
11 documentary evidence which I thought was, you know, the
12 evidence I thought was a really good job, I was really
13 impressed with the amount of effort that had gone into
14 that. Having recently done something similar myself
15 with the European data I know how difficult it was so I
16 was very impressed with what was presented this
17 morning.

18 On figure 4.1 which I think this morning
19 turned up as slide 21, is it possible to see that
20 again? Yeah, this was a very interesting graph which,
21 you know, shows a relationship that none of us
22 expected. But I went back and looked at the data here.
23 Study 425 was performed in 1977. The other data set is
24 nearly as old. So similar vintage there, but when we
25 look at these they were very short replicas, 3 to 5

1 minutes long and in 425 they loaded about half the
2 product from a 50 kilogram bag. And in the other
3 studies they were handling several complete bags. And
4 maybe the work tasking using, measuring out the product
5 from part of a bag was very different to using complete
6 bags so those sort of aspects we need to consider as
7 well.

8 I think another comment I would make was
9 using data from about 30 years ago to do risk
10 assessments now and the composition of modern granular
11 formulations is probably much better, probably a lot
12 less dusty so these data might be quite conservative
13 anyway.

14 I think it's also worth noting that the 3 to
15 5 minutes duration in these studies illustrates why you
16 need to describe the relationship so you can estimate
17 exposure form whole day work tasks. And it's probably
18 important to recall in our deliberations that the new
19 data will be more representative of the full working
20 day and in those cases extrapolation is necessary. It
21 won't be so much of going from short replicates to try
22 to estimate what happens, you know, a representative
23 working day but it will be looking at extrapolation to
24 different application rates or different product
25 concentrations which may be, have slightly less

1 uncertainty than this situation has.

2 One of the other figures in the document was
3 figure 4.2, I don't think we need to get the graph up
4 for that, but it was, it looks at the rest of body
5 outer dosimeter relationship for studies 1003 and 448,
6 that they didn't seem to have the same sort of
7 relationship that the overall regression had. And it
8 seemed to be influenced by, very much by a single point
9 from Study 428. I just think we need to look at those
10 sort of aspects as well.

11 Slide 20 from this morning which was figure
12 4.4 I think in the original evidence, Doctor Johnson
13 made one of the points that I was going to make,
14 looking at the yellow dots from Study 1011, if you took
15 those in isolation maybe the slope is closer to 1,
16 that's what I thought when I was looking at those
17 before. I think further inspection of the data here is
18 also interesting. 1004 and 1011, they are similar in
19 age, they're both from, well one's from 1992, the
20 other's from 1994, both products contained 5% active
21 ingredient, both were done outdoors, one in the U.S.,
22 one in Canada, don't expect any difference from there,
23 both involved workers who were separately monitored
24 over short periods again so each of those dots
25 represents about a 10 minute work period so there's

1 some issue with that. But they're similar in that
2 respect. There were differences in the environmental
3 conditions, 1004 was done under winds speeds of, some
4 of the replicates with wind speeds recorded as 6 to 8
5 miles per hour and others of them 10 but Study 1011 was
6 done under much windier conditions and all the wind
7 speeds were recorded as above, being above 10 miles per
8 hour. That's might have had a partial reason for this
9 sort of relatively higher exposures in the second
10 study. There were also differences in the product
11 packaging. 1004 used 10 pound bags and 1011 used 50
12 pound bags. Again this could have contributed to the
13 differences observed between the two studies with the
14 larger bags being much more difficult to handle.
15 Another difference was the product. In 1004 it was an
16 insecticide and that in 1011 is a herbicide. This
17 suggest that to me that there may be some differences
18 in the equipment being filled and to continue this
19 comparison it would be helpful to have descriptive
20 details of the tasks done. Unfortunately we don't have
21 those in the database and I looked for the details of
22 the tank and the hopper size to gain some idea of the
23 sort or equipment being used. For Study 1011 it's
24 given as 450 to 1,150 and I assume the units are
25 gallons but I can't remember what they were specified,

1 but we don't have any information for that parameter
2 for the other study so we can't really compare. But
3 these are sorts of the issues that I think are
4 important.

5 And I, you know, the point I'm trying to make
6 is that when we're doing these analyses we're not
7 comparing like with like and care is needed when
8 looking at the relationships within studies.

9 Just briefly, would additional variables help
10 to explain some of this variation we see? Well I think
11 it, maybe they would but I think there are issues
12 because a lot of the additional parameters recorded in
13 the studies, if we start including them we do have
14 problems with multi-collinearity which we, when we start
15 adding a lot of related variables into the analysis so
16 that we have to be very careful of that. And the other
17 sort of point of caution I think is that when we're
18 looking at the variables to see if they helped us give
19 a better description of the determinants of exposure,
20 then they have to be sensible in terms of, from the
21 regulatory perspective and one can imagine that some of
22 the parameters are not very helpful from that point of
23 view. Statistically they may be interesting but from a
24 practical point of view they're not.

25 I expect the new data will possibly help to

1 inform on these sorts of relationships because there's
2 obviously a lot of issues when looking at the PHED
3 data. It would be nice to design sort of an
4 experimental approach but I am persuaded by the
5 arguments that the new data should really be more
6 descriptive and that would really meet the requirements
7 if the other objective that such studies really should
8 involve applications representative of what workers'
9 typical practices are rather to have some artificial
10 element built into them. And I think that's all I have
11 to say for the moment.

12 DR. HEERINGA: Thank you very much.

13 Doctor Kim.

14 DR. KIM: Being from a school of public
15 health when I look at this data, the data sets or the
16 charts that EPA presented, what comes across my mind is
17 that assuming proportionality between exposures and the
18 amount of active ingredient handled is like the problem
19 ecological fallacy. The ecological fallacy is the
20 assumption that all members of a group have the same
21 characteristics of the group at large. So something
22 like, you know, all students from Harvard have higher
23 SAT scores than students from Cornell but if you take a
24 random sample you find that there's a student from
25 Cornell who has a higher SAT score than a student from

1 Harvard.

2 And in the figure shown in section 4 of the
3 background document provided by EPA we see evidence of
4 this. In other words, across studies we see a linear
5 trend but if we look at each individual study
6 separately the assumption of linearity doesn't seem to
7 hold. And Doctor Johnson discussed this in his
8 comments. However if unit exposures are going to be
9 applied in a risk assessment management context then it
10 should hold across studies and scenarios. In other
11 words it should be generalizable. I think that the
12 AHETF, the task force is moving in the right direction
13 by collecting data for a wide range of pounds applied,
14 a variety of locations, MUs and diversity of workers
15 and equipment can be used to better assess this
16 proportionality, the assumption of proportionality.
17 However a controlled study may be much more informative
18 for teasing out this relationship.

19 My final recommendation is that strict
20 adherence to linearity might not be the right approach.
21 In PPPA models when we construct them we use scaling
22 laws for cardiac output, ventilation, using body weight
23 to the power of .75 and this can, when we look at
24 volume of tissue we don't necessarily use those, the
25 power law. However these are, these relationships are

1 established from empirical measurements and are
2 determined using log or regression analysis. These
3 laws hold across and within species and is a
4 generalizable law that has been determined empirically
5 and used widely. Something similar may be helpful
6 here.

7 DR. HEERINGA: Thank you very much Doctor
8 Kim. And Doctor Popendorf.

9 DR. POPENDORF: Well, let me begin with
10 pointing out a couple of weaknesses in the analyses
11 that are, have been done. I mean given the data they
12 were a good job but I think the problem lies with the
13 existing data. For instance the first figure in the
14 presentation was that was slide number 4 from Reinert
15 and Severin, good correlations but again that really
16 wasn't active ingredient handled if you look at the x
17 and y. It really was a prediction of dose rate as a
18 function of concentration of what was being sprayed.
19 So, you know, good data, different, obviously a
20 different correlation.

21 The second point is the weakness of a lot of
22 the other data. Again, what was there, for instance
23 figure 4.2, you're looking at a very narrow range. You
24 know, looking ahead to some of the discussion I think
25 in question 6 where they're designing the study and how

1 big a range do you need to answer some of these
2 questions? We don't really have an obvious measure of
3 the variability of the individual points that I was
4 talking about yesterday. And if you consider how
5 variable those points are you're looking at a, that is
6 the y value, you're looking at the x value over a range
7 of 10x and the variability in the y's could be, you
8 know, 5, 10, the same kind of magnitude, you really
9 can't test the validity of that test, you know, you're
10 just looking at those points but those points aren't as
11 accurate or as precise as they appear on paper.

12 So, you know, we definitely would need to
13 look for opportunities within PHED to look over a wider
14 range of x's and that looks like it'll be designed into
15 the new database.

16 I think as a point, you know, and some people
17 kind of question the idea, do we really need to use
18 that active ingredient handled? And I think in order
19 to extrapolate to other pesticides that may be at
20 different concentrations, if you change formulation
21 you're going to end up with different amounts or
22 perhaps the actual amount applied on per acre and if
23 some user applies a given number of acres you need to
24 be able to do some kind of extrapolation to those other
25 settings. And I think the logic that was pointed out,

1 I mean it's intuitive that it should be related, it's
2 been used, it's sort of that default value that we kind
3 of have to go with.

4 But I can fully agree with the comments in
5 terms of the issues of equipment. That's got to make
6 some differences and I think you need to really
7 consider the equipment within the categories that are
8 being proposed. Perhaps look at that and narrow those
9 definitions of what you're, what is being used within a
10 category so that, you know, you might end up with a few
11 more categories but you'll be able to make better
12 predictions because of the influence and very easy to
13 get a 10x difference just due to equipment that has
14 been pointed out.

15 You know, I was going to suggest, you know,
16 the rate of exposure issue kind of like the Severin
17 paper, that seems to be something to look at in the
18 future, whatever that design is, the critical event
19 type of thing, the handling of some number of bags or
20 valves or that type of experience is certainly
21 important. Perhaps the speed of what is being used and
22 it might be the rate at which you're actually putting
23 the material on. You know, that could differ if you're
24 certainly in a tractor environment, the fast you go
25 the, no wind at least and average in various

1 directions, the further away that mist is going to be
2 so you could predict speed having an affect. If you go
3 to a manual type operation, biocide type operation and
4 speed could certainly again sort of dilute the affect
5 of exposure. There's a lot of possibilities that could
6 be looked at. I think you just sort of consider at
7 this point that amount of active ingredient handled as
8 the default consideration.

9 I think I mentioned earlier that, my
10 observation about the, when the slope is greater than 1
11 so that's sort of on the record, given what I just said
12 about how reliable is the slope, I don't know how good
13 that conclusion is. It's just strictly an observation.

14 I think completes my comments.

15 DR. HEERINGA: Thank you Doctor Popendorf.
16 Comments on this particular question of
17 proportionality. Doctor Landers.

18 DR. LANDERS: I'd like to support the
19 comments that were made earlier by Paul Hamey. As I
20 mentioned yesterday, not all sprayers are the same and
21 so we discussed that.

22 I would like to support Doctor Kim in his
23 ecological fallacy. In engineering we have engineering
24 fallacies. I'll give you a quick example, nothing to
25 do with the SAT scores but as a fellow academic we all

1 know that Princeton is in New Jersey and we leave them
2 out of the debate. We have to be fair.

3 Anyway, closed transfer systems appear to be
4 heralded as the answer to everything, you know, just
5 stick one of these things on and we've protected the
6 man. I would like to point out that in California for
7 example where they have such legislation, removing a
8 dripping probe from a pesticide container puts the
9 operator at greater risk than removing a sheathed
10 probe. And so not all closed transfers are the same.

11 So what is to be done about this? Well my
12 recommendation to the two groups is, when they consider
13 closed transfer system that, or any other engineering
14 control, that some form of matrix system be developed,
15 either looking at high risk/low risk components or
16 looking at ancient versus modern, some simple system so
17 that you can create a better system. Thank you.

18 DR. HEERINGA: Doctor Landers made a very
19 interesting point. When you talk about sort of a
20 qualification or some quantification of relative sort
21 of risk level across technologies within these, even
22 these exposure scenarios, the 30 that are proposed for
23 the AHETF. So you would just have some sort of graded
24 system that might be part of the database that could be
25 used like the data quality measures are currently.

1 DR. LANDERS: Yes, indeed.

2 DR. HEERINGA: That's a good suggestion.

3 Thank you. Other comments from other presenters?

4 Yeah, Doctor MacDonald, Peter.

5 DR. MACDONALD: I'd just like to ask
6 Doctor Hamey to give some examples. You referred to
7 some variables that were more of statistical and less
8 practical interest and I was just wondering what you
9 had in mind there. It seemed that everything we've
10 talked about is practical.

11 DR. HAMEY: It's just when you look at the
12 database there are about 80 or 90 different variables
13 for each application that recorded crop height, boom
14 height, wind speed, boom width, number of nozzles, boom
15 pressure and some of those things. I don't think as a
16 regulator we have much understanding as to what are the
17 different practices in reality and if we want, we
18 decide it's a parameter that is useful and we want to
19 have some control over it, then we have very difficult,
20 great difficulty in making recommendations and
21 enforcing recommendations that people can follow.

22 DR. HEERINGA: Cynthia Hines.

23 DR. HINES: Yes, I would just like to
24 actually commend the task force for recognizing that it
25 is important to test this assumption of proportionality

1 and to try to work that into their data collection
2 efforts and recognizing that you do need to improve the
3 variability in the amount of active ingredient handled.

4 I agree with Doctor Kin that this is
5 something critical that needs to be looked at because
6 we are normalizing everything by pounds of active
7 ingredient handled and it may not always be
8 appropriate. And so it's time and it's something
9 that's concerned me over the years to look at this to
10 the extent that we can.

11 DR. HEERINGA: David Miller.

12 MR. MILLER: Yeah, just to add on I guess
13 to Doctor Hamey's and Doctor MacDonald's, in terms of
14 things that are of regulatory interest, a 60 foot boom
15 width versus a 20 foot boom width or so, that's not
16 something that is, can be, well, I mean a farmer's
17 equipment is a farmer's equipment so that's a lot less
18 manageable in terms of by label changes than for
19 example a variety of other things.

20 DR. HEERINGA: But in that context I think
21 Doctor Landers' suggestion that across the whole array
22 of equipment within a scenario that there may be some
23 method based on expert judgement to sort of qualify the
24 relative possibilities. Within that we'd still have
25 enormous variability but that might go a long way to

1 sharpening this out.

2 Let me ask the panel, in the context of this
3 generic system, database and its use in the regulatory
4 framework that you've heard about, do we agree that
5 this proportionality assumption is probably the
6 conservative assumption, the straw man against which
7 everything else would be tested? Are there consensus
8 on that? Dallas you'd better

9 DR. JOHNSON: I'm always bothered by this
10 word proportional because it's not really being used as
11 proportional. If something's half of something else
12 they're proportional. But it's more than being
13 proportional, it's the slope is equal to 1. And I
14 think the planned data will allow one to test that
15 assumption and I guess that, I think it's something
16 that should be looked at and then I guess people will
17 use it the way they want to use it.

18 DR. HEERINGA: Doctor Popendorf.

19 DR. POPENDORF: Yeah, think it might help
20 to support that default if the Agency were to develop
21 a sort of physical model or a rationale based on
22 physical mechanisms of exposure that would be the
23 background document if you will. It doesn't have to be
24 extensive but, you know, why would the amount handled
25 be a predictor? Some of the critical events that

1 Doctor Hamey mentioned, for instance in some scenarios
2 there's no good reason to think that it would in some
3 exposure scenarios. But if you had a rationale for
4 each scenario then I think it would help to justify
5 that, whatever assumption you do go into, active
6 ingredient is your probably most common category.

7 DR. HEERINGA: Doctor Bucher.

8 DR. BUCHER: In thinking about how this
9 might be utilized by the Agency I think it might be
10 worthwhile for the Agency to prospectively consider
11 what kind of information you could generate from this
12 kind of database that would convince you that you
13 should depart from this assumption of linear
14 proportionality, because I'm afraid that if there are
15 not really compelling data generated and there's lot of
16 data points that are sort of randomly scattered around
17 on the map, that it's going to be difficult for you to
18 really decide where you would depart from this
19 assumption and where you wouldn't.

20 DR. HEERINGA: Doctor Lu.

21 DR. LU: I think this proportionality
22 issue may have something to do with how the pesticide
23 is being mixed in the spray. So it definitely is not a
24 default assumption. It's probably a case by case
25 scenario. I look at all the graphs that the Agency

1 provided in the background documents. It kind of
2 strikes me that if you pay close attention, the cases
3 or scenarios that are close to the linear
4 proportionality will be for the application I remember
5 as open cab air blast. I mean the r square is close to
6 1 and so on and so forth. And I think there's a reason
7 for that because again I have a very limited field
8 experience and all the field experience that I have was
9 associated with fruit tree growers. They use air blast
10 in the field and what happens is the active ingredient
11 is OP or other pesticides they use, even if mixed in a
12 tank and then being blown out by the big engine as the
13 tractor hauls the thing along the orchard.

14 So if you think about an exposure scenario
15 it's close to uniform exposure because it's become a
16 smog of aerosols. And probably you can assume that
17 each aerosol if you were able to collect each droplet
18 they'd probably have an even concentration across the
19 air.

20 So in that scenario if you look at the graph
21 that EPA produced they're close to the r equal to 1
22 slope. That's the only case that I can see. Again it
23 has something to do with the way the pesticide has been
24 applied but it definitely is not a default assumption.

25 DR. HEERINGA: Other comments from panel

1 members? We'll turn to David Miller and Matthew. do
2 you fee that we've addressed this question? Are there
3 any concerns or is there any information that you feel
4 you were looking for but you haven't received?

5 MR. MILLER: Maybe just one, I've heard
6 kind of some different things about definitely not a
7 default assumption and others that it seemed not an
8 unreasonable assumption. Obviously we'll be looking at
9 it in terms of the, some of the data we have but of
10 course the AHETF, they will also, as you'll hear more
11 about tomorrow, part of their secondary objective for
12 that is to determine, well essentially get better
13 information about whether proportionality with a
14 certain power. So I think we'll probably be visiting
15 that some as well

16 DR. HEERINGA: Okay.

17 MR. MILLER: tomorrow.

18 DR. HEERINGA: Okay. Any additional
19 comments at this point?

20 DR. JOHNSON: Just one, Steve. The good
21 news is that it doesn't really matter as long as, I
22 mean as long as it's proportional with respect to some
23 slope.

24 DR. HEERINGA: Right.

25 DR. JOHNSON: It doesn't matter that the

1 slop, whether the slope is equal to 1 or not, you can
2 still predict risk, or still predict exposure.

3 DR. HEERINGA: It just changes your
4 threshold of risk.

5 DR. JOHNSON: Right.

6 DR. HEERINGA: Yeah.

7 MR. MILLER: I guess one of things too
8 that is kind of key on that in terms of was if most of
9 them tend to have essentially, when you do the log log
10 the x values, the exponents are less than 1, that's
11 tending to be protective at the upper. So maybe a
12 default of 1 it tends to be protective in that aspect
13 if we do agree that it doesn't curve up like that.

14 DR. HEERINGA: Doctor Popendorf.

15 DR. POPENDORF: As you say; if we agree.
16 And you know I made my point earlier about it might but
17 can we really believe the data that's there? We don't
18 really know.

19 DR. HEERINGA: I'd like to do a little
20 group thinking here because we are a little past 1:30,
21 I'm going to make a liar out of myself, I think we
22 would have the prospect of finishing today if the
23 presenters who are scheduled for tomorrow morning are
24 ready. And I want to, I don't, wouldn't want to push
25 that ahead without them but I'd like you to be thinking

1 about that between now and the time that we finish our
2 discussion of the next question because that will be a
3 decision point.

4 And so I think that the representatives who
5 will be speaking on behalf of the Agricultural Handlers
6 Exposure Task Force and also I think, David, you have a
7 short presentation too which you said is very short,
8 it's more of a lead in, thinking about whether we might
9 do that and then finally address that last question
10 this afternoon. We won't make that decision now but be
11 thinking about that and obviously we won't, I won't
12 make that decision on my own, I'll confer with you at
13 our break.

14 But let's, at this point move on to the next
15 question which is question number 5, having to deal
16 with within worker and between worker variability. And
17 Matthew, if you would read that into the record please.

18 MR. CROWLEY: This is Matthew Crowley,
19 Health Effects Division, EPA.

20 The proposed AHETF study design does not
21 include true worker replicates and is not intended to
22 examine the issue of variability within workers. The
23 AHETF notes that to appropriately investigate this
24 issue would require significantly more sampling and
25 resources. They propose however that their single dat

1 exposure distribution results can be used to evaluate
2 longer term multiple day exposures by placing
3 reasonable limits on expected interclass correlation
4 coefficients, the ICC. They indicate that, from their
5 own research and review of the literature the ICC is
6 likely to be between 0.3 and 0.5 over relatively short
7 periods of time, for example seasonal, and likely to be
8 even lower over longer periods of time.

9 Please comment on the AHETF's approach to
10 estimating the number of samples needed to determine
11 within worker variability and their inclusion on the
12 importance of measuring such variability in their
13 proposed studies.

14 DR. HEERINGA: Thank you very much. And
15 Ken Portier is the lead discussant on this question.

16 MR. PRESENT: I'm going to preface my
17 comments by saying, you know, the question asked is a
18 two part question. One is on the sources of
19 variability on these observational exposure studies and
20 whether the within worker, what's the importance of the
21 within worker or within handler variability term. And
22 then the second question you're asking us to comment on
23 sample size determination as it relates to clustering
24 or studies.

25 And I think the second question on sampling

1 really belongs in our discussion on question 6. And my
2 comments on the clustering sampling, the sample size
3 issue really needs to follow the presentation that was
4 planned for tomorrow morning. After talking with the
5 panel and Doctor Holden it's clear we kind of need to
6 see that presentation before I jump into my comments.

7 So I'm just going to concentrate on the first
8 part, on the within worker variability issue and maybe
9 let the other members of the panel comment on that and
10 then we can have our discussion on whether we want to
11 move forward with the Agency and the AHETF's
12 presentation before we really get into a kind of a full
13 discussion of sample size. And I think my panel
14 members probably agree to that.

15 So with that I'm going to start with my
16 discussions on sources of variability and observation
17 exposure assessment.

18 After listening to the presentations and
19 discussions it's clear that exposure data collect from
20 observational studies has the potential to address
21 three sources of variation. First there's among
22 handler variability, that is variation among different
23 individuals doing the same or similar task, typically
24 under differing environmental or other conditions.
25 Everyone agrees that this variability is necessary to

1 measure and is a basic component along with the
2 estimate average in almost any risk assessment.

3 The second component is the within handler
4 variability. That is, variation among different
5 measurements on the same individual doing the same or
6 similar task, almost certainly under different
7 environmental or other conditions. We say different
8 environmental or other conditions to stress that these
9 are not true repeated measures in the sense of an
10 experimental study since study settings are never
11 completely under our control, and in any case, since
12 repeats have to be done at different times. We expect
13 other factors that could affect exposure to have change
14 during that time period.

15 The concern with repeated measurements is
16 that because all the measurements are taken on one
17 handler then the resulting values should display a
18 positive correlation. The AHETF proposal argues fairly
19 strongly that this source of variation is unimportant
20 and/or too expensive to measure given the objective of
21 the resulting data to support benchmark or minimal
22 adequacy requirements for tier 1 and tier 2 risk
23 assessments.

24 The third component is the within study
25 variability. That is, variation among measurements

1 taken on different handlers within a specified study.
2 This is referred to as the cluster affect and the
3 concern is that handlers doing the same or similar task
4 at one site may produce similar exposure values because
5 the measurements are taken under common environmental
6 or other conditions. The measure of similarity used
7 for within study variability is typically the
8 interclass correlation or the ICC, and the range of
9 interclass correlation is estimated to be 0.3 and 0.5
10 for measurements taken over a short period of time. I
11 needed to get this, yeah it's on there, sorry, I have
12 to get slide out because for me to read this equation,
13 you know, it's nice but, and statisticians can't do
14 anything without equations right? I could wave my
15 hands, would that help? This is under EPA SAP, EPA,
16 January '07 and it's the PowerPoint slide. That was
17 good. The folder, EPA January '07 in the PowerPoint
18 slide. This is one of three memory disks, right, next
19 slide.

20 Okay, thus the true model for MU exposures is
21 a modification of equation 1 in the procedures for
22 determining the required number of clusters and
23 monitoring units per cluster to achieve benchmark
24 adequacy, which is one of the background documents that
25 was provided to the panel.

1 So here we have an equation for the adjusted,
2 what's called the normalized exposure as a function of
3 an overall mean, in this case the log geometric mean,
4 plus a variance component for cluster, plus a variance
5 component for workers within a cluster and then a
6 variance component for repeated measures within workers
7 within a cluster. Just click it one more time so you
8 don't have to read all that stuff, it's just the same
9 thing that was in the document. But the basic idea is
10 that if we, you know, the kind of the overall
11 conceptual model involves all three of these and what
12 the proposal basically says is, throw out the last one,
13 my r , i , j , k since we're not really interested in that
14 particular variance component. Okay, so I wanted to
15 have that just so we'd know that and that's going to be
16 useful tomorrow or later today when we talk about
17 sample size.

18 The AHETF arguments to de-emphasize within
19 handler variability in Section 5.3 are clear and
20 compelling. In particular they argue that repeated
21 measurements on a single handler are difficult to do,
22 typically are done without strong controls on other
23 factors that can impact measured exposure and the
24 resulting repeated measurements would be expected to
25 demonstrated low correlation, that is a RWW term

1 between 0.2 and 0.4. The RWW term essentially relates
2 to the variability of the repeated measure term, okay?
3 This is not the ICC term, that relates to workers
4 within a cluster. This is the repeated measures
5 correlation of variability term. The between handler
6 data which will populate the AHED database is expected
7 to support tier 1 and tier 2 risk assessments. For
8 such assessment the focus is on cumulative exposure
9 over long time periods. The distribution of individual
10 long term cumulative exposures will be best described
11 by the between handler distribution regardless of
12 whether this RWW term is 0 or 1, and I think they make
13 a very good and clear argument and description of why
14 that's the case. So I don't have any problem with
15 that.

16 The also argue that the between handler data
17 distribution could be used to simulate both within
18 handler and between handler variability in any
19 probabilistic Monte Carlo risk assessment by specifying
20 and drawing from some RWW distribution. So, we don't
21 necessarily have to know what this repeated measure
22 correlation is, if we've got some idea of what its
23 distribution looks like in the population we could kind
24 of simulate correlated repeated measurements in a Monte
25 Carlo simulation and I think that's a clever way to

1 actually utilize the between handler data to handle
2 within handler variability.

3 All of the above I understand, I can see the
4 industry viewpoint on the issue of within handler
5 variability. But myself and some of the others who
6 have talked about this issue can't help but feel that
7 EPA could be missing an opportunity by not pressing or
8 investing in some limited repeated measurements. And
9 our justification for allocating time and resources to
10 limited repeated measurements is as follows. So, you
11 know, there's always a 'but' in these things, right?
12 And here's the 'but'.

13 Current literature on which within handler
14 correlation is, the current literature on within
15 handler correlation, or on which the correlation's
16 values are estimated is small and problematic. This
17 doesn't, this literature does not provide strong
18 justification for limiting the range of RWW, something
19 which might be needed if indeed the AHETF approach is
20 used to incorporate within handler variability in
21 future assessments. So it's kind of one thing to say,
22 well, we have these four or five studies and we can
23 kind of guesstimate some values from this, but my
24 experience on this panel is that kind of a statement
25 usually doesn't cut it when you're trying to justify a

1 fairly complex risk assessment. And we're thinking
2 that, you know, real data would make an easier
3 argument.

4 Any probabilistic risk assessments, we want
5 to, we want, will want to incorporate both within
6 handler and between handler variability. The AHETF
7 approach is always going to be weaker than an approach
8 which is founded on estimates that are backed by
9 actual data. The actually data case is always an
10 easier case to make than kind of an assumption based
11 case.

12 While the AHETF states little interest in
13 examining potential determinants for factors of
14 exposure, EPA and other researchers will definitely be
15 looking to use these data for exactly this reason. The
16 best data for identifying exposure factors is to have
17 measurements taken under different levels of the
18 suspected factor on the same individual using that
19 individual as a block. So any matched measurement
20 study is always going to be more powerful than any
21 other kinds of study. So if I've got repeated measures
22 of an individual doing the same task under different
23 conditions it helps me determine whether that condition
24 really affects exposure or not.

25 So from a study point of view for other

1 users, and I understand where AHETF is coming from on
2 this, but I'm saying other users who are going to look
3 at this database as a gold mine, they'd be happy to see
4 some limited repeated measures in there.

5 So some limited repeated measurements on
6 handlers in the database could result in more powerful
7 studies of the importance of exposure factors. Adding
8 limited repeated measurements should be relatively
9 cheap, especially when compared to the cost of starting
10 a new study, say bringing a new location and/or
11 recruiting new handlers. Once the study site is
12 established and handlers are recruited and documented
13 it's relatively easy to get permission to take
14 measurements from multiple times. I see no reason to
15 examine repeats that occur at very separate periods of
16 time, which would really increase the cost
17 significantly. But same day or next day repeats would
18 provide kind of the most information for the least
19 additional investment.

20 Fifthly, I don't see repeated measurements as
21 creating an ethical or other issue with the Human
22 Subjects Review Board review. To get one measurement
23 on the handler will require approval by that handler.
24 Since these are work tasks that the handler is
25 typically engaged in, there's little extra about

1 getting a repeated measurement that would raise a flag
2 in front of a review board. You've already asked the
3 person to participate, you've gotten their approval,
4 it's a, I just don't see them really getting all upset
5 with that.

6 For these reasons we think the AHETF should
7 reconsider their strict stand on repeated measurements.
8 In the long run a better understanding of factors that
9 affect exposure can lead to better understanding of how
10 to mitigate risk and lead to better risk assessment.

11 And I think I'll stop it at that point.

12 DR. HEERINGA: Thank you very much Doctor
13 Portier for the introduction. At this point Cynthia,
14 Cynthia Hines will be our next associate discussant.

15 DR. HINES: Thank you very much. I think
16 Ken covered a lot of major points so I might just
17 expand on a few.

18 I have a lot of mixed feelings about this
19 because in my own research I have very much valued
20 doing repeated measurement designs. And I kind of can
21 relate to Dana over here who had to kind of give up on
22 the biomonitoring when it's near and dear to her heart
23 for the database. I feel your pain.

24 I also have, because of my field experience I
25 really am very familiar with the challenges of trying

1 to do these studies in agriculture. And at a minimum,
2 trying to do a repeated measure study within one of
3 these scenarios is going to mean at least doubling, you
4 know, of course the number of measurements you make.
5 So if you have say 25 persons in your scenario that's
6 50. You know, it would even be better if you could,
7 you know, triple that. And there are going to be a lot
8 of agricultural situations where getting even 50 people
9 is going to be challenging and even getting two
10 measurements within your study period.

11 I think some of the other challenges that are
12 posed, that have been mentioned in terms of the
13 frequency of collecting these measurements is a very
14 good question. You don't have a lot of control over
15 that sometimes in agriculture in terms of how often
16 these applications are made. So you may be waiting a
17 couple of weeks for the next one, you may be, you know,
18 it's just very challenging.

19 And also of course analytic costs go up and,
20 you know, and the task force here hasn't really spoke a
21 whole lot about that but I would imagine that's one of
22 the considerations when you're doing as much monitoring
23 as they are in terms of whole body dosimetry and face
24 wipes and hand washes.

25 So I can really see that trying to do

1 repeated measurements on all the scenarios may not be a
2 feasible proposition, even if it's data that would be
3 very valuable and of interest to all of us.

4 What I am wondering is if there is, and I
5 haven't thoroughly looked at this, but is there a
6 possibility of looking at maybe one or two scenarios
7 that might be of interest to EPA or, and the Task
8 Force, where that scenario or those couple of scenarios
9 could be looked at from a repeated measures study
10 design where the conditions in the field and the number
11 and frequency of applications might lend itself to that
12 kind of study design? And so I might encourage that
13 you think about that before totally giving in on the
14 whole idea of losing information on our within worker
15 variability.

16 I agree with Ken that once, and from my own
17 experience, that once a person has consented to a
18 study, that getting a second or even a third
19 measurement is usually not a problem. Usually your
20 barrier is getting them to agree to the study and
21 accepting the procedures. I think once they're
22 comfortable with that, unless you're doing something
23 very onerous, I don't think that will be a big issue
24 for you in a repeated measures study frankly. And I've
25 never had any problem from a Human Subjects Board as

1 long as the burden is not excessive.

2 There, in reading through the Task Force
3 plan, and you may have changed some of the parameters
4 since you wrote the document, but at one place I read
5 that if a person were to, a consented person were to
6 withdraw from the study that you would consider taking
7 a person who'd already participated once and having
8 them in a sense do a repeated, have them participate a
9 second time, like a repeated measurement on just a few
10 of the people in your study. And I guess I would kind
11 of want to suggest that you just, discourage you from
12 doing that, that if you're not really going to commit
13 yourself to a repeated measures study design, then just
14 get unique individuals and not end up with a hybrid,
15 because I've seen those situations and then they get
16 really messy in terms of, do we treat this data
17 independently, do we not? That kind of thing. And
18 then sometimes observations get thrown out. So you
19 might think about that.

20 And then a couple of my other, or some of my
21 other thoughts really, like Ken said, I think relate
22 more to sample size issues. So maybe we should defer
23 on that. I will only just mention a couple of things
24 because maybe you can address them in your, the Task
25 Force could address them. And there was something in

1 your document about biasing toward conditions that
2 might yield higher exposures and I don't know if you'll
3 be talking about that but if you could go into that a
4 little bit. And I'd also like to hear a little bit
5 more about the evidence supporting the, the importance
6 of the geographic distance of the clusters and why you
7 feel strongly about that.

And I think that's it.

8 DR. HEERINGA: Thank you very much
9 Cynthia.

10 MR. MILLER: I wonder if I might

11 DR. HEERINGA: David Miller.

12 MR. MILLER: just a couple of questions.
13 At some point it might be a good idea to see if the AG.
14 Handler Task Force might be willing to come up and just
15 give some of their thoughts on it.

16 I did have a few questions if I could just in
17 relation to what's kind of been said before. It that

18 DR. HEERINGA: I wonder if we should hear
19 from the remaining associate discussants. Can we do
20 that and then go back? Let's, if you don't mind,
21 Doctor Kim.

22 DR. KIM: My comments will be short. The
23 point made by the Task Force regarding the focus of
24 their monitoring program and the intended use of the
25 AHED is well taken. Their statistical analysis is
convincing and I appreciate the simulation exercise
that was presented with the technical summary.

I commend the detailed work of the AHETF, the
Task Force and the presentation of this material.
However their data does not address within and between
worker variability. Their conclusions are based on
work done by Doctor Crimalt's group and Doctor Fenske
in response stated that it would be helpful if EPA
would conduct its own analysis to determine a range of
values. I don't know if anyone has already done this
but I'm assuming not because it was not reported in the
EPA's background document.

So, I calculated the within worker
correlation coefficient using the repeated measures
data presented in figure 5.1 or the EPA's background
document. I estimated the variance components using a
one way random affects model for 10 individuals with a
number of repeated measurements ranging from 2 to 6.
The total number of observations was 39 and I obtained
a within worker variance component of 0.4 and a between
worker variance component of 2.5 and the within
subject, or within worker correlation coefficient of
0.9. Thought this is a different finding from the
assumptions made by the Task Force, it lies outside the

1 range of within worker correlation coefficients.

2 So there are two things here. One, the
3 assumption is wrong. Secondly there's not much
4 information gained from repeated sampling within an
5 individual so your conclusion is supported with this
6 quick analysis. However, before making final
7 recommendations it would be prudent to examine the
8 within worker correlation coefficient for various
9 exposure scenarios.

10 On the flip side, repeated exposure studies
11 are, I think needed to better understand biomonitoring
12 data. As discussed yesterday, biological differences
13 between individuals is important for interpreting
14 biomonitoring data. Because of the physiological
15 differences between individuals, because they vary much
16 more than within an individual, such as body weight,
17 metabolism, height, et cetera, a repeated exposure
18 study would be very helpful for understand the
19 relationship between passive dosimetry and biological
20 monitoring data.

21 DR. HEERINGA: Thank you very much Doctor
22 Kim. Doctor Johnson.

23 DR. JOHNSON: Yes, I, initially I didn't
24 feel like I had much to contribute to this discussion
25 and I probably still don't but I'm not smart enough to

1 keep my mouth shut.

2 The, I thought the Task Force made a good
3 argument and I could live with that. I thought Doctor
4 Portier also made a good argument and I could live with
5 that. And so I'm not really quite sure where I come
6 down.

7 One thing that might be of some interest is
8 the relative cost associated with collecting the data.
9 I guess I assume that a lot of the cost is associated
10 with measuring the amount of chemical that are in the,
11 whatever garments you collect, that that's probably the
12 major source of expense. There may be some expense in
13 getting to a particular study location but it might be,
14 I don't know how these costs compare to one another.

15 I thought Doctor Portier was suggesting that
16 you didn't need to collect the repeat data, you didn't
17 have to add the same number of repeats on every subject
18 and you didn't have to actually repeat every subject,
19 that you could repeat fewer subjects. But then that's
20 in contradiction with Doctor Hines who wants to have
21 every subject done the same number of times. I guess
22 given those two options I would, if the major objective
23 is to measure this interclass correlation I would be
24 inclined to go with Doctor Portier's recommendation. I
25 think the, you've got these three variance components

1 to measure and there are certain numbers of degrees of
2 freedom associated with those and so in trying to make
3 a decision I guess I would try to do something that
4 would sort of give me equal numbers of degrees of
5 freedom associated with each variance component. And
6 the only way you could do that is to not have the same
7 number of samples for each individual and/or the same
8 number of samples of workers within each study. So it
9 may not be feasible to do that but I do think you can,
10 if you do replicate the individual workers and if the
11 major source of cost is associated with analyzing the
12 data that you collected for the chemicals deposited,
13 then it might not be necessary to measure each
14 individual the same number of times within each study
15 and within each worker.

16 DR. HEERINGA: Yes, Cynthia Hines.

17 DR. HINES: I just wanted to clarify. I
18 agree, you don't have to measure the same person the
19 same number of times. I was more concerned about the
20 situation where you have just a few people that you've
21 done repeated measures on and it's too small to do
22 anything with. But you certainly don't have to have a
23 perfectly balanced situation.

24 DR. HEERINGA: Okay, your statement is, if
25 you're going to do it, do it right so you'll get

1 utility from the data that's there?

2 DR. HINES: Yeah, that's right.

3 DR. HEERINGA: Right. Doctor MacDonald.

4 DR. MACDONALD: Yeah, I also didn't think
5 I was going to have anything to say but I'm going to
6 give some preliminary remarks on some ideas I'm trying
7 to put together for the discussion of the sample size
8 question.

9 But we've got really three different types of
10 design going on here. If you're trying to sample a
11 total population economically you use cluster sampling
12 because once you get into one situation you can pick up
13 a few more subjects fairly cheaply. So that's really
14 the purpose of cluster sampling, to lower the total
15 costs. And that assumes that the cost of going to a
16 location and getting the workers signed up then it's
17 relatively cheap to do more workers or even to do
18 repeated measures on one worker.

19 If however you want more detailed precise
20 information on specific scenarios then you do what's
21 more commonly called stratified sampling and there you
22 pick the scenarios that you're most interested in and
23 you make sure you get enough observations within each
24 scenario. And that's a quite different objective from
25 cluster sampling.

1 Then on the third level a number of people
2 here in the room, on the panel and on the Task Force
3 seem to have an interest in the different levels of
4 variability in their own rite, within worker, between
5 worker, between scenario, between machinery. And
6 that's a different kind of question yet again and
7 requires a different approach to the sampling design
8 and I think some of the confusion is that we're looking
9 at the one database and the one design to answer all
10 three types of questions, and that the sort of
11 recommendations you make on sample size depends really
12 on how important you think the three different
13 questions are.

14 DR. HEERINGA: Thank you very much Peter,
15 I appreciate that comment. I think it's just everybody
16 recognizes that simply because we are not measuring
17 them to estimate them, these components of variance
18 aren't disappearing, they're present in the overall set
19 of measurements, we just can't differentiate them and
20 put that information in the differentiated components
21 to different uses. And there clearly are different
22 uses as you point out.

23 David Miller, you had a, you wanted a follow
24 on question for the panel?

25 MR. MILLER: Just one of the things that

1 the HSRB brought up during June was in terms of they
2 brought up this specific issue in terms of consistently
3 neat or consistently sloppy workers. As you know, the
4 way we, in PHED right now there are true replicates but
5 they aren't counted when we do our analysis that way.

6 I guess I had a question for Doctor Chambers
7 just in terms of kind from what you've heard here in
8 terms of some of the recommendations or thoughts or
9 suggestions, in terms of repeat measurements, maybe a
10 limited number, et cetera, do you have any thoughts on
11 the HSRB perspective on that in terms of, if we go
12 with, one, if it goes one way, how is the HSRB going to
13 feel versus another way for example?

14 DR. HEERINGA: Doctor Chambers, are you
15 comfortable answering that?

16 DR. CHAMBERS: Thank you for giving me a
17 segue because I was going to ask for a little bit of
18 time to philosophize on it anyway.

19 There are two things that have been brought
20 up at this meeting that I think are going to raise some
21 significant flags with the HSRB. One is the scenario,
22 excuse me, the scripted business that came up yesterday
23 and then it's repeated measures.

24 I've been working with the HSRB for its first
25 year of existence and I'm on the science side obviously

1 and I'm speaking now for the ethicists which I'm not
2 one of. But their main concern seems to be that we are
3 putting people at a higher level of potentially risk
4 than they would be in our, their normal occupations.
5 And even though they may agree to an informed consent,
6 Ken, there are still concerns I think that the people
7 are being exposed to more than they normally would be.
8 And I'm really not, I can't answer your question,
9 David, I really don't know how they're going to come
10 down on that but that's clearly the types of
11 discussions that have occurred over the past year.

12 What I was going to suggest and I don't know
13 whether this is out of line, Bill Jordan, or not but,
14 you know, if the HSRB could be thinking about those in
15 a highly generic way beforehand, the scripted idea, the
16 scripted exposure and repeated measures without having
17 a particular proposal in front of them, we did that
18 kind of, you know, when we first reviewed our, the
19 previously done studies we came up with a list of
20 criteria by which we would judge whether or not these
21 were scientifically valid studies or not.

22 If we divorce the consideration from any
23 particular proposals and come up with the philosophy of
24 the group on scripted exposures and on repeated
25 exposures, I'm wondering if that might be a little bit

1 useful. And I would say if that is considered a useful
2 suggestion it should be done in all haste really before
3 any of these proposals get brought up. That's just
4 something that occurred to me over the last couple of
5 days here.

6 DR. HEERINGA: Doctor Portier.

7 DR. POPENDORF: I want to kind of reply on
8 one thing. On the repeated measures I guess if this
9 were an experimental study I'd agree with you, because
10 if we were doing a scenario where we're asking the
11 worker to repeat for the purposes of measurement only a
12 task over and over again, you'd be exactly right, we'd
13 be increasing their exposure by forcing them to redo an
14 exposure event.

15 But this is an observational study, we're not
16 asking them to do anything other than what they would
17 normally be doing. So there, you know, whether we turn
18 our back and measure them or not they're going to still
19 do that next load. And so I see no, actually I see
20 decreased exposure because they've got this stupid
21 whole body thing underneath that's intercepting the
22 dose. So if anything we're mitigating exposure on
23 these events. So I guess I would kind of argue that.
24 I mean I could see the experimental setting, it's a
25 mouse, you're jabbing it and you're aggravating it and

1 it's unethical but with a person who's going to be
2 normally doing the task they're going to do it whether
3 we measure it or not.

4 DR. CHAMBERS: This is Jan Chambers
5 again. My understanding and you all correct me if I'm
6 wrong, but my understanding is if it's a strictly
7 observational study it will not come to HSRB, it will
8 only be brought to us John Carley is nodding his head
9 that's correct. And it's only if it's something
10 beyond observational and semi-experimental that it will
11 be brought to us. And these scripted things are not
12 going to be absolutely observational, regular routine
13 things is my understanding.

14 DR. POPENDORF: That may be true for the
15 biofoulant study, the other task force, but I think for
16 this one, I don't think they're planning to do anything
17 scripted, they're going to do things, I mean that was
18 my understanding and maybe we need that clarified. But
19 for the handler/loader kind of scenario that's not
20 scripted. For the other task force that is going to be
21 scripted and I agree with you on that because there you
22 are asking them to do something in a scenario that they
23 might not normally be doing it.

24 DR. HEERINGA: Cynthia Hines.

25 DR. HINES: Yeah, I think this is a major

1 source of confusion right now, is how much of the Task
2 Force current plans are scripted. Because when you
3 read through the proposal there are definitely scripted
4 elements in there. And while I agree in a purely
5 observational study, repeated measurements should not
6 have an HSRB issue, if you do throw in that scripted
7 element and you are intentionally affecting or changing
8 that exposure, that's a different story. So if we
9 could get some clarification on this whole issue of
10 scripting that would help.

11 DR. HEERINGA: Yes, Bill Jordan.

12 DR. JORDAN: I'm Bill Jordan from the
13 Pesticide Office at EPA. There is a continuum between,
14 in the ways that one can design research. At one
15 extreme research could be for exposure purposes could
16 be designed in a very scripted way where, for example
17 one of the studies that was discussed the other day was
18 a jazzercise study in which people wore whole body
19 dosimeters and they were told exactly what body
20 movements to do.

21 They were to spend so much time crawling
22 around on the floor, then they were to roll over, then
23 they were to do jumping jacks or something like that.
24 They were doing that on a floor where a pesticide
25 residue was present and then the whole body dosimeters

1 were removed and the quantity of the residue that had
2 moved from the floor surface with which they had had
3 contact into the dosimeters was used as a basis for
4 estimating potential exposure. That's at one extreme.
5 I think we'd all agree that's a scripted study.

6 At the other extreme people who are engaged
7 in research could go out, find a field that had been
8 treated and ask the workers, hey, may we have your t-
9 shirt at the end of the day? May we have your pair of
10 pants? Step into the booth over here and we'll trade
11 new pants for old ones and there would be simply a
12 collection of those items of clothing and the same kind
13 of analysis might be done on the clothing residues
14 measured. And there might be an interview with worker
15 to say, how long did you work there and there might be
16 an interview with the farmer to collect information
17 about how much was in the spray tank and so on and so
18 forth. That latter one would be observational.

19 What the AG. Handler Exposure Task Force is
20 doing falls sort of in between and each one of them
21 will be looked at on a case by case basis to figure out
22 whether as one of you mentioned, the scripted elements
23 dominate to an extent that we would consider it
24 intentional exposure, i.e., that the exposure that the
25 subjects in the research receive would not have

1 occurred but for their participation in the research.

2 In thinking about the AG. Handlers Exposure
3 Task Force protocols, at least the ones that I'm
4 familiar with, what they are doing is that they decide
5 on a particular scenario that they want to evaluate,
6 they decide on a particular chemical that they want to
7 evaluate, they go out and find a farmer who's willing
8 to be a cooperator in the research and agrees to hire a
9 crew or use employees working with that farmer, to, or
10 even a research facility, to apply that pesticide to
11 that crop at that rate and allow the researchers then
12 to work with the crew who would be engaged in the
13 handling activities to collect the necessary
14 measurements of exposure, hand rinses, whole body
15 dosimeters, face wipes and so forth.

16 Now the farmer is not going to agree to
17 participate in that research if they don't need to do
18 the pesticide treatment or if the pesticide treatment
19 is the wrong one or somehow or other it's not
20 appropriate for the particular site. But the decision
21 of the researchers about what they need is driving to
22 some extent the decisions about what pesticide is used
23 and therefore influencing the potential exposures
24 received by the subjects in the research. That
25 characteristic is in my view, and I think in the view

1 of the other folks at EPA, sufficient for us to say
2 that the subjects are participating in research that
3 involves intentional exposure.

4 But I will happily concede to anybody who
5 wants to discuss it that, yes, indeed there is a range
6 of research designs and this one falls in the middle,
7 closer to that line between observational and
8 intentional exposure. But as a policy matter we are
9 choosing to apply our regulation in such a way as to
10 call this research that involves intentional exposure.

11 DR. HEERINGA: Thank you very much Doctor
12 Jordan. Doctor Landers, did you have a comment? Any
13 additional comments from panel members at this point in
14 time on the issue of within worker and between worker
15 variability and I guess we led off into the notion of
16 replication. Yes, please identify yourself.

17 DR. LEIGHTON: Yes, this is Tim Leighton
18 from the Antimicrobials Division. I want to clarify
19 the Antimicrobial Task Force.

20 The scope of some of the studies in the
21 antimicrobial perhaps will be observational. For the
22 antimicrobials we do have industries such as metal
23 working fluid where the workers are there every day and
24 we can actually go in and monitor them. So some of the
25 ones in the antimicrobial will actually be potentially

1 observational.

2 DR. HEERINGA: Okay, any followup on that?
3 I'm interested in this distinction and and I won't drag
4 it out here on an IRB2 between something that's
5 observational as opposed to experimental. I thought if
6 it were research it would be reviewed and you maybe
7 exempt it.

8 DR. LEIGHTON: And another good example in
9 the antimicrobial is the pressure treatment of wood
10 where there is an existing facility, the worker is
11 there every day, they're using a compound that we
12 actually have analytical techniques for so we can go in
13 and monitor those workers without changing what they're
14 doing that day and get the measurements. So there are
15 some example of what we hope will be observational
16 studies.

17 DR. HEERINGA: Thank you very much.
18 Additional comments from the panel on this? We, it
19 sort of led us off into another area. David Miller.

20 MR. MILLER: Yeah, I wonder if I could
21 just follow up on a couple of

22 DR. HEERINGA: Absolutely.

23 MR. MILLER: Okay. One of the suggestions
24 that came, or thoughts that came up on the panel which
25 we hadn't thought of before, but it might be possible

1 to have repeated measurements on only a number of
2 scenarios, or not all of them in other words.

3 And the question I guess I had, I'm not a
4 subject matter expert, but are there certain scenarios
5 where you think it might be more likely to get repeated
6 measures because you get that sloppy versus neat worker
7 affect? In other words, I'm just making it up but it
8 might be backpack sprayers, you might be kind of more
9 likely to get high correlations from day to day within
10 a worker versus, and I'm just making this up, aerial
11 applicators, they may be much more less likely. So one
12 of things I'm wondering is is it possible that if there
13 could be repeated, or at least thoughts about repeated
14 measures on scenarios which you think are most useful?

15 DR. HEERINGA: Paul, Paul Hamey?

16 DR. HAMEY: Well I haven't got an answer
17 in terms of the behavior of workers. But it might be
18 useful to try and relate it to the actual use patterns.
19 So if you have scenarios where workers will not be
20 repeatedly exposed to the same chemical then perhaps
21 it's of low interest. But if you have a scenario where
22 they repeatedly use the same chemical then it's of more
23 interest.

24 And something that would come to mind, again
25 not knowing the use patterns in the U.S., but if I was

1 looking at this in the U.K. I'd be particularly
2 interested in orchard applications where there are
3 spray programs that have repeated applications every
4 sort of 10 or 7 days of the same chemicals.

5 So that might be a consideration.

6 DR. HEERINGA: Thank you. Doctor Lu.

7 DR. LU: It sounds like Mr. Miller has
8 some sort of fear factor that are kind of associated
9 with your study design, mainly because of the Human
10 Subject Review.

11 But I remember the protocol for the IRB
12 protocol, there is a component that, yes, you need to
13 assess the risks that are imposed on the human subject,
14 but also there's a component of benefit. So what
15 happens is that we all value repeated measurements and
16 that's why a lot of people that conduct this type of
17 research, we kind of move from a cross section of study
18 design to longitudinal, longitudinal meaning that you
19 are going to repeat taking samples from the same
20 participant over a period of time.

21 And we recognize that's the important step
22 forward because we will get a lot of information from
23 this type of a repeated measurement study that will
24 never exist in the cross sectional. So that's a huge
25 benefit and I will argue that, yes, we do put

1 additional risks on the participant because instead of
2 giving us one urine sample they're going to give us 24
3 urine samples over a one year period of time.

4 But is the risk reasonable because the
5 benefit will outweigh the risk? I don't know whether
6 the HSRB ever can see the benefit component when they
7 look at not just this study but all studies.

8 DR. HEERINGA: Doctor Barr.

9 DR. BARR: I just want to clarify
10 something. As a sitting member on one of CDC's IRB
11 boards, there's a distinction between risk and burden
12 to the participant. Collecting urine is a minimal
13 risk, especially if it's urine samples collected as a
14 part of their daily duty. Now you may be imposing more
15 than minimal risk if you're asking them to do an
16 application where they wouldn't otherwise be doing it
17 or you're asking them to apply a chemical that they
18 wouldn't otherwise be applying. Then you might be
19 putting them at more risk but it still might be less
20 than minimal risk.

21 So by adding additional sample collections
22 you're not putting more risk into the study but you are
23 placing more burden on the participant. And so the
24 compensation to the participant would actually have to
25 equal the burden that you're placing on the

1 participant.

2 DR. HEERINGA: Doctor Landers.

3 DR. LANDERS: Am I right in thinking
4 yesterday we decided that the reason for these tests
5 was for the registration purposes of a new product?
6 And therefore if it was, or if it is, sorry, then if
7 it's a new product then if they're going spraying for
8 example, then the application of that product would be
9 for experimental purposes, the crop would have to be
10 destroyed and therefore we would be conducting an
11 experiment by its very nature rather than an
12 observation.

13 Would you like to comment on that?

14 DR. PORTIER: I think the thing is that
15 they're not going to do this with new chemicals,
16 they're going to do this with a common one that they
17 understand a lot about the properties and that is in
18 current wide use and they're avoiding the new chemical
19 issues and worrying about the physical issues. So I
20 don't think this database gets into that. Its utility
21 will be toward the new chemical but not its
22 measurement.

23 DR. HEERINGA: Doctor Curwin.

24 DR. CURWIN: I mean this whole subject
25 seems a bit off topic and I wasn't going to bring this

1 up because it is off this variability topic. But on
2 the human subjects side of it, it's my understanding of
3 the new data that would collected would be on existing
4 chemicals which I think was just clarified. And what I
5 understand the manipulation part of it would be is the
6 amount of active ingredient handled and that's what
7 they're trying to get at. So the way you would
8 manipulate this is either by manipulating the
9 application rates or the acres applied. But my
10 understanding is that this would still be within the
11 labeled rates, the label use rates.

12 So in terms of maybe increasing the potential
13 subject's exposure that may be the case, they may be
14 asking the farmer to apply a little bit more than they
15 normally would have but it's still within the
16 acceptable risk level that's been established by the
17 EPA already. So if we're to believe the risk
18 assessments that the EPA has done on these existing
19 chemicals then their actual risk shouldn't be
20 increased.

21 DR. HEERINGA: Doctor Chambers.

22 DR. CHAMBERS: Just real, real briefly
23 here, let me just clarify that the HSRB is not an IRB,
24 the HSRB looks at the IRB approvals that have come down
25 and everything. The HSRB has almost no experience

1 right now at looking at protocols. All we've been
2 doing most of the time is looking at completed studies
3 and so we're really kind of going into protocols right
4 now. And that's why I suggested that perhaps now is a
5 very, very good time to try to get some philosophical
6 tenets down for HSRB on why they would approve repeated
7 studies, scripted studies and that sort of thing before
8 they have to look at an individual study and judge it
9 in the context of a new proposal.

10 DR. HEERINGA: Thank you very much Doctor
11 Chambers. At this point in time Doctor Portier.

12 DR. PORTIER: I just wanted to get back to
13 one last clarifying statement which I think Doctor
14 Dallas said. The statisticians really don't care if
15 things are not balanced in this data set. We just want
16 measurement somewhere so if you have the measurements
17 we can estimate it.

18 And so to re-emphasize the balance issue is
19 not really a big concern for us. It's an existence
20 proof than an amount proof, right? We'd just like to
21 see some there so we could estimate those values. And
22 I think Doctor Kim's little study that he did on the
23 side kind of makes the point that I made, that you have
24 literature that says it's this, and yet your own data
25 says it's that. You're going to need something that's

1 going to tie this down a little bit firmer if you're
2 going to use it at any point in the process. And we
3 can, I can at least envision some situations where
4 you're going to want that source of variability.

5 MR. MILLER: I know Mr. Villanueva has a
6 quick question but just an immediate followup on that,
7 would one possibility be to go deeper into PHED and
8 essentially look for essentially the, that kind of
9 information? There are repeated measures there and
10 would that help inform I guess, instead of that range,
11 .2 to .5 or something like that? Would that assist
12 in

13 DR. PORTIER: Yeah, yeah, I thought of
14 that and the reason I didn't make that recommendation
15 is because the general feeling we has is the level of
16 control that you've had within the PHED data is fairly
17 low. You either have control or you have a lot of
18 measurement, is really what you need to be able to do
19 this. And you don't have a lot of measurement on
20 external factors.

21 You didn't have a lot of control in the
22 generation of the data and so I'm not sure that
23 exercise is going to produce a lot of useful
24 information. The AHED on the side is going to have a
25 lot of control and a lot of exposure factor

1 measurement. So you've got two good things going for
2 you there and all we're asking you to do is think a
3 little harder about what we're going, we're going 85%
4 of the way or 90% of the way, another 10% and you're
5 going to have a real jewel of a database that's going
6 to allow you to look at all three sources of
7 variability.

8 That's all I'm kind of, trying to say here is
9 that we're, you're almost there and we don't want you
10 to falter at that point. At least that's my feeling
11 and I think that's supported by the rest of the panel.

12 MR. MILLER: Can I do a quick followup on
13 that? Just, you had mentioned before one possibility
14 was essentially to do a limited number of replicates,
15 I'm making the number up, 10% or something like that.
16 Do you see kind of in terms of do you have any thoughts
17 in terms of the balance if they increased the number of
18 replicates by 10% but decreased by a certain percentage
19 the number of different individuals? I mean I guess
20 it's a cost/benefit type thing. Is that something
21 that, do you have any idea in terms of numbers?

22 DR. PORTIER: I think we'll get into that
23 in the discussion of sample size.

24 MR. MILLER: Okay.

25 DR. PORTIER: I mean I, I didn't really

1 plan to address repeated measures in the sample size
2 question, I was going to go on the assumption that you
3 weren't going to be interested in it and we'll, we
4 would discuss, but I think given a little bit of time
5 we can probably give you some recommendation on that.
6 At least some approach recommendation on how to handle
7 it.

8 DR. HEERINGA: Mr. Villanueva, do you have
9 question for the group?

10 MR. VILLANUEVA: Yes. Actually Doctor
11 Kim's exercise got me thinking and I was, with the ICC
12 I'm being bounded for 0, between 0 and 1, if we have 1
13 then repeated measures doesn't really matter at all, we
14 might as well just have sampled another individual, 0
15 meaning that there's no correlation between the
16 measurements.

17 And I guess what I'm thinking about is the
18 variance components that Doctor Kim mentioned, I think
19 they were about equal worker to worker and then within
20 worker. I think, or were they similar?

21 DR. KIM: If I recall it looks like .4 for
22 within and about 3 for between.

23 MR. VILLANUEVA: Okay, yeah, well, that's
24 even, I think that's probably even better but the real
25 question is, is I guess thinking about the benefits of

1 repeated measures. If you just have, it really gets
2 down to estimating that variance component within
3 worker and the question I'm thinking is, is there any
4 reason for the panel members to think that the within
5 worker variation is actually going to be larger than
6 the worker to worker variation? And if not we can just
7 use as a surrogate the worker to worker variation to
8 represent the within worker, being a conservative
9 estimate. So saying that, you know, they're not
10 correlated at all and you're just as likely to measure
11 another person.

12 DR. PORTIER: You know, in looking at the
13 data on the graphs I mean I got the feeling that the
14 within worker variability is going to be less than the
15 between worker variability. But that's, that's hard
16 because everything we see is confounded by study
17 condition too and so it's a little bit, and it's a
18 little bit hard to be able to make a real firm
19 statement on that.

20 But I wouldn't be surprised if the within
21 worker and between worker variability are very much the
22 same in this situation. I mean my feeling is that the
23 RWW is probably close to 0, much closer to 0 than it is
24 to 1, in the sense that, you know, repeated
25 measurements on the same person are very much like

1 repeated measurements on other workers. And that you
2 haven't lost a lot by assuming that these repeated
3 measurements were independent in the previous risk
4 assessments. I haven't seen anything that really makes
5 me worry about that too much. Maybe Doctor MacDonald
6 can comment on that too.

7 DR. HEERINGA: Doctor MacDonald.

8 DR. MACDONALD: Yeah, Doctor MacDonald,
9 I'm just thinking there's got to be some compromise
10 between us sitting around and trying to decide on
11 whether a certain scientific fact is true or not and
12 insisting that the new database have 25 repetitions of
13 every worked and every situation. There's got to be
14 some sort of compromise and certainly a limited number
15 of directed studies just might be enough to establish
16 whether this is going to be a reasonable assumption or
17 not.

18 But I am concerned by what Doctor Portier
19 said, that of course that anything you do is going to
20 be, the results will depend on the conditions of that
21 study and you always worry about generalizing to
22 others. But at least it would be better than us just
23 trying to guess the answer.

24 DR. HEERINGA: Doctor Kim.

25 DR. KIM: Just a followup on that. Yeah,

1 I agree that the whole purpose of that analysis was to
2 demonstrate that, okay, let's just not go, we'll
3 proceed forward based on studies that were done by
4 other people but actually do a few studies ourselves,
5 or EPA, to estimate the within subject variability or a
6 correlation coefficient.

7 DR. HEERINGA: Steve Heeringa here, I want
8 to follow up on Doctor MacDonald's comment too. And I
9 think that in terms of the model that Doctor Portier
10 put up, that's a pure random affect for the individual
11 and I don't think we can ever measure that in any sort,
12 because we are always confounding the fixed affects of
13 the measurement, the boom length, the temperature, the
14 wind, with those individual measurements. We can never
15 sort that out so unless you have a utility for that
16 pure individual affect or you're willing to work with
17 those individual affects contaminated by a particular
18 application scenario you need to think carefully about
19 what you're getting out of that. And I know Doctor
20 Hines, you probably have to do that all the time in
21 your work. But I think that we have to realize that
22 everything we've seen, those random affects, even if
23 you estimated them with models are probably going to be
24 cross contaminated by the fixed affects in that
25 geometric mean.

1 So that's just a, that'll come up I think in
2 the sample size discussion.

3 What I'd like to do at this point is I think
4 I'd like to call a break for 15 minutes. And if I
5 could have a little pow-wow with the EPA scientific
6 staff and the AG. Handler Task Force, the Microbial
7 Task Force who are here this afternoon and are going to
8 be doing presentations. Just to see, I want to make a
9 quick decision as to whether we have a green light to
10 go ahead today or whether we would be putting anyone at
11 a disadvantage in terms of preparation and coverage.

12 So if we could just, those people can meet up
13 here.

14 We'll come back at 10 minutes to 3:00 please.
15 (WHEREUPON, there was a recess).

16 DR. HEERINGA: Okay, let's please have our
17 seats and we'll get ready to start again.

18 Let me first explain where we have come down
19 in terms of the progress of the agenda. As Myrta said
20 at the start of the meetings it is a floating agenda so
21 we are able to move things around. But I had a
22 conversation just prior or just after the start of the
23 break with sort of the principals from the Task Force
24 and from the EPA and from a few representatives of the
25 panel.

1 And where we have come is that we would like
2 to use the balance of the afternoon to actually begin
3 to have two presentations, one of them a short one by
4 David Miller and Matthew Crowley and then following
5 that up, that was actually scheduled for late today,
6 and then following that up we'll have another major
7 presentation by the Agricultural Handlers Exposure Task
8 Force, Larry Holden, which gets into some more of the
9 statistical issues related to the exposure assessment
10 and the research plan development of the AHETF.

11 That'll leave us probably I suspect about an
12 hour and then we will have time for questions of
13 clarification. If we do begin our discussion of the
14 sample size charge question this afternoon I would
15 expect to return to that tomorrow morning. Everyone
16 was in agreement that it would be beneficial what the
17 case, to return here tomorrow morning after everyone's
18 had a time to digest the information covered today, to
19 think up any new questions, develop any new sort of
20 responses or clarifications. So we would have that
21 session tomorrow morning. We would finish our
22 discussion of the sample size question tomorrow
23 morning, have a general wrap up set of questions so
24 that everybody leaves here comfortable that they've had
25 a chance to present their positions and we've had the

1 kind of exchange we've had this afternoon.

2 After three days we have to get a life, you
3 know, and we're still talking here about sample size
4 issues after three days. But it's been great and I
5 really appreciate everybody's contribution.

6 So at this point in time then what I'd like
7 to do is I'd like to ask David Miller and, or Jeff
8 Evans to give their short presentation.

9 MR. MILLER: Yeah, this is just a real
10 short one or so, really kind of geared more toward an
11 intro to the next one which you'll hear from industry.
12 It just kind of recaps a little bit about what we've
13 talked about before and what the industry is going to
14 be presenting next.

15 Just to begin on that slide number 2, just
16 it's kind of a quick recap of the exposure topics
17 discussed to date. It began with a historical
18 perspective on handler exposures, it went through some
19 of the developmental, development of PHED as well as
20 its use as a generic database, its function, kind of
21 where it came from, the data that went into it, why it
22 was generated to begin with, et cetera. There was also
23 a discussion of passive dosimetry and biological
24 monitoring and then also hand washing methods. And
25 then kind of the EPA presentations ended with a

1 discussion of the proportionality between pounds AI
2 handled and exposure and discussed generally the kind
3 of the inter exposure concept and how that's central to
4 a lot of kind of what we've done.

5 Just the next presentation is introduced, to
6 introduce is the Agency's asked the panel to discuss
7 the limitations of the present data and how additional
8 data which is proposed to be collected by the Task
9 Force can improve our ability to assess worker
10 exposure.

11 What we're not asking is the panel to review
12 the plan proposed by the Task Force for addressing
13 these issues.

14 The panel received as part of its package,
15 two specific documents that are going to relate to the
16 Task Force presentation next and again it'll blend in a
17 little bit to some of the other documents, in
18 particular the intra versus inter-worker variability.
19 But the two documents, I won't read them, one was just
20 a technical summary and the other the specific document
21 on clusters and monitoring units. So basically a
22 statistical simulation and a general plan for what the
23 Agency is, what the Task Force is proposing to do.

24 The primary goal is the collection of worker
25 exposure monitoring data and its incorporation into a

1 generic database that will define exposure
2 distributions. That's stated in the Task Force
3 documents.

4 The AHED you've heard about and the idea
5 behind it is to have the ability to estimate individual
6 exposures for a single workday given two pieces of
7 information, mixer/loader/applicator pesticide handling
8 scenario as well as the amount of active ingredient
9 handled.

10 The purpose of the presentation you'll hear
11 next from the Task Force is to discuss their data
12 development plan that's consisting of both kind of
13 their overall plan which relates to the first document
14 that went through. And then the other issues related
15 to sample size and its adequacy. It deals with the
16 number of sites, the number of subjects per scenario
17 and activity and also kind of how that relates to the
18 previous discussions in terms of the repeated measures.

19 DR. HEERINGA: Thank you very much Mr.
20 Miller. At this point in time, unless there are any
21 questions from the panel, Jeff, did you have anything
22 to add at this point?

23 MR. EVANS: No, I mean only to add that
24 the sample size was probably one of the biggest issues
25 raised by the HSRB and it's a constant battle with the

1 agencies and data doers so this is an extremely
2 important part of the program for us.

3 DR. HEERINGA: Thank you. We'll devote
4 adequate time to it. Okay, at this point then I'd like
5 to request that the presenters for the AHETF, if they
6 were willing to come forward. Do you have a microphone
7 there Doctor Holden?

8 DR. HOLDEN: Thank you Doctor Heeinga.
9 Let me get this set up here, okay.

10 This is the second part of a two part
11 statistical presentation I guess that I'm sure you all
12 were looking forward to. That wasn't supposed to be
13 funny but I guess it is.

14 DR. HEERINGA: Doctor Handwerger before he
15 left asked us to videotape this.

16 DR. HOLDEN: Oh no. I'm sorry, my
17 mistake, yeah, I'm technologically ignorant here, there
18 we go.

19 In this presentation I was going to cover the
20 sort of the last three, not the last three issues but
21 the last three issues that we wanted to discuss today.
22 The sampling methods and the description how we're
23 actually going to sampling or proposed. Doctor Portier
24 has assured he's got the solution to all these problems
25 so we're all set. And secondly, a discussion of the, I

1 would say, in a sense an example or an example of how
2 we propose to at least start to address the issue of
3 the goals to help determine the sample sizes and I
4 think that you'll see that we feel strongly that there
5 ought to be some goal other than just collect data.
6 And then finally just a few slides outlining the
7 general, if you want to call it kinds of things we're
8 going to be talking about in the scenario summary
9 analyses that the Task Force is planning to provide
10 along with the documentation for AHED if you will.

11 Here we go with my little population diagrams
12 again. What we're starting off is with this term
13 monitoring unit which I'm sure that people are
14 scratching their heads and wondering where that term
15 came from. And it's basically what we are referring to
16 as not necessarily the individual, but the set of
17 conditions that we select from this target population
18 and the resulting exposure measurements and everything
19 else we measure.

20 So a monitoring event is actually probably a
21 better term. I think the Agency or someone threw that
22 up but I actually like that term better. This term
23 monitoring unit was sort of patterned after the main
24 sampling unit which was just to try to find something a
25 little more neutral that replicate which has sort of a

1 different meaning, depending on who you talk to and the
2 context.

3 So we are obviously going to be taking
4 samples from this target population but these samples
5 are not going to be what's called a probability sample,
6 or not a true probability sample anyway. In other
7 words we're not saying, unfortunately, not saying that
8 the, that we have enumerated either implicitly or
9 explicitly all the possible conditions and are sampling
10 from them with some sort of known probabilities, be it
11 completely simple random or otherwise.

12 We sort of feel that in order to do that we
13 might have to have some approach, or one approach
14 possibly would be to do something like a multi state
15 sampling that's typical for so many surveys where one,
16 and it's important to describe this, where the, we
17 might start off by making a list of all the counties
18 let's say in which this scenario was, is being used and
19 maybe time periods in some sense, maybe weeks, months,
20 whatever it is, some unit of time, some increment of
21 time. And then randomly select from those as the first
22 stage. We might first, we might do that by first
23 enumerating or getting some idea about the, how many
24 workers that might be inside that and select the size.
25 We might use some sort of stratification, I think

1 Doctor MacDonald mentioned that, some sort of
2 stratification approach, whatever might be appropriate
3 to increase precision.

4 Once we've got the sample of county/periods,
5 I'll use that term, then one would proceed probably
6 within that county and conduct a large number of
7 activities designed to ultimately get down to
8 enumerating the number of potential monitoring events
9 inside this county. This may involve, and probably
10 will involved doing it maybe several more stages of
11 sampling, but in some sense we'd get down in some sort
12 of organized probabilistic way into a smaller set of
13 potential monitoring units and then randomly select
14 those.

15 What you'd end up with is a sample of
16 monitoring units when then you would use to conduct
17 your study. These monitoring units, or at least the
18 exposure results from the monitoring units because this
19 probability sampling is unequal, would each have
20 associated sampling rates. In other words there would
21 be some rate such as, that would represent in a sense
22 the relative numbers of individuals in the target
23 population that each of those monitoring events
24 represents. And it might not be, if it was a simple
25 random sample the rates would all be the same so it

1 falls out and then that's why, I mean, that's what you
2 oftentimes see in your statistics 101 textbooks.

3 So we, this approach is not the only
4 approach. I've done surveys like this and they're
5 complicated, expensive and there may be simpler ways to
6 do things. But in this, this approach is quite costly
7 as you can imagine and most of the costs are overhead
8 costs. Going from the county/periods, the first stage
9 is very simple, it's not usually, it doesn't take very
10 much effort but the real costs come in the lower stages
11 within the counties in this example here. And so we've
12 got a lot of costs.

13 Now for larger surveys like the ones in which
14 I've been involved with we have like 1,500, 2,000
15 sampling units that you end up with eventually. It's
16 worthwhile for small precision. I think we're talking,
17 and hopefully we're talking about sample sizes a little
18 bit less than that per scenario in which case the
19 overhead cost might really swamp out the monitoring
20 costs so it might be quite expensive. And what that,
21 when those kind of costs come that means that something
22 has to give and usually it means that there's fewer
23 scenarios or fewer replications per scenario or
24 something.

25 There's also issues that go along with many

1 surveys or anything else that, the timing of activities
2 and whether you do it randomly in some sense and such
3 and the selection of workers and travel expenses. When
4 you start selecting things with some degree of
5 randomness it becomes a bit more difficult.

6 There's delay in monitoring activities and in
7 setting this up, and it would delay the start of
8 additional collecting but these are things that can be
9 worked around given enough time, effort and money.

10 The AHETF studies, however we do have studies
11 in the database already that were acquired. Some were
12 already, there are some in there that were generated
13 from the methodology we're, I'll be discussing that
14 were collected previously. So whatever is done, it
15 might a little bit like a, not very cost effective to
16 worry too much about a real complicated survey sampling
17 design, say multi stage design and then throw it in
18 with some other data that were collected under
19 different ways. It makes it, it's almost your, you
20 have apples and oranges in here, very expensive apples
21 and a little bit cheaper oranges but you still have,
22 you're mixing and matching there. You might be able,
23 it may be difficult.

24 So what we're, have currently done, and for
25 the studies that have already been collected and what

1 we're proposing to continue, barring Doctor Portier's
2 solutions, are what I'm going to call purpose and
3 diversity sampling which is actually something that
4 exists and I just didn't make it up. And in a sense
5 this is a, the monitoring units that we use are
6 actually selected based on judgement and I'd like to
7 state here ultimate availability, I mean sometimes you
8 just can't find something and you take what you get.
9 But ultimately with judgement. And the selection of
10 process, so that's where the purpose of aspect comes
11 from, not selected randomly but purposely. And in
12 addition the purpose is to increase the diversity of
13 some or various factors. And the factors that we're
14 most interested in decreasing the diversity of are
15 amount of AI handled which you've already discussed
16 previously, location and a date, what I'm going to call
17 cluster and we'll get to that in a second, and workers
18 which you've already discussed, was discussed in the
19 last session and it was also, I mean there's some
20 issues there about whether we continue that process or
21 not but that's currently what we're doing.

22 And then in most other respects were some
23 caveats which I'll describe later, the monitoring of
24 the workers, will perform their tasks pretty much in
25 the normal fashion.

1 Let me just briefly describe the methodology
2 that's used, at least the target that's used for
3 diversifying the amount of AI handled. First the Task
4 Force determines the, a range of AI, I'm sorry, amount
5 of active ingredient handled under the scenario based
6 on expert opinion and other information they have
7 available. This range is truncated a bit. On the
8 upper end it's my understanding that there is some,
9 it's so difficult to find situations, even though
10 theoretically something that high pounds per active
11 ingredient can be handled it's hard to find something
12 that, an example of that actually being done and so
13 that might tend to truncate the upper end a bit and but
14 we're talking levels of about a ton per day per user.
15 So we're still talking pretty large amounts that we do
16 include in the database.

17 The, on the lower end oftentimes it has to be
18 restricted, at least for the surrogate compounds that
19 we're using because we want to stay above the limit of
20 detection. So if you get too low then the exposures
21 are just too low to measure, reliably anyway.

22 So what's left in the middle we're calling
23 the practical range of AI handled and the, well we,
24 basically what we do is try to space out the pounds per
25 AI handled pretty much equally spaced on a logarithmic

1 scale so I'll call that logarithmic spacing for a short
2 cut. That's pretty much what we do there with the
3 understanding that it's not always possible to get that
4 exact but that's sort of a target.

5 Now we mentioned the, this issue has been brought
6 up time and again over the last several days so it's
7 probably no surprise to many of you, the, we found,
8 both in our data and analysis and it's very, it seems
9 very common in a lot of data that we will do an
10 exposure monitoring study and you have individuals that
11 are being used that are within the same general area,
12 the same general time and perhaps more importantly,
13 being done in the same study with the same study
14 monitoring personnel, that there tends to be, and even
15 when the pounds per active ingredient handled are
16 exactly the same, you tend to have study effects if you
17 want to call each one of those things a study, you have
18 these study effects or cluster effects that might be
19 different.

20 These may be due to known factors, equipment
21 was a suggestion. An example of these study effects to
22 me seemed to be very evident in some of the data the
23 Agency presented earlier on on the PHED data. And I
24 think Doctor Pependorf referred to that quite often so
25 that's great.

1 So this, this kind of, but it's also factors
2 that we really don't know what they're due to. I mean
3 there's so many factors that differ, I mean any two,
4 any two studies you get on locations you're going to
5 find hundreds of variables which differ. Some of those
6 with your subject matter expertise you might be able to
7 say are reasonable candidates for the cause. But
8 there's really no easy way to prove it without doing an
9 experiment, trying it under those conditions and those,
10 that's the need for future, for designed experiments in
11 my opinion. But nevertheless we find these effects,
12 it's if, given, I'm sorry, given that that's the case
13 it seems like what the ideal thing to do would be to
14 diversify or to not sample any more than one person
15 within one location at one time. In other words, one
16 person per study would seem to be a great way to go to
17 reduce this artifact of sampling.

18 But that's not very cost effective as I think
19 Doctor Portier mentioned earlier in the last session.
20 It's oftentimes cheaper, there's a cost, there's an
21 advantage to once you've found a location there's a lot
22 of effort involved, a lot of overhead into getting a
23 study set up. The additional cost per unit is
24 substantial but it's all, but it's a heck of a lot
25 cheaper than going out and doing another study and

1 getting one person. So there is a cost savings
2 involved in doing multiple people per study. And I'm
3 sorry I gave Doctor Portier credit for that and I think
4 it was Doctor MacDonald who mentioned that.

5 In any event our clusters or our monitoring
6 units tend to come in clusters and these clusters
7 typically represent a study. Although in a few cases
8 we have a single GLP study that might have multiple
9 locations spread out over a period of time in which
10 case that study would have multiple locations but in
11 many cases a study and location are synonymous.

12 And because of this fact we tried to, what
13 we're trying to do is when we sample a scenario is try
14 to have multiple clusters at least per study, we don't
15 want to get studies with only one cluster or two. That
16 just is just is asking for trouble because the cluster
17 effects make life very difficult. And so we always,
18 there's a balance then between number of clusters and
19 number of units per cluster that's going to be involved
20 in the sample size.

21 And finally, I know this issue's been
22 hammered to death already in the last session, but we
23 are, have been in the past been attempting to not get
24 repeated measures or multiple measurements per worker,
25 certainly not within a small space of time or space

1 because we feel that that information is just not as,
2 we're being really redundant because there, it just may
3 be correlation between those values so we have been
4 attempting, our goal had been taking only one
5 individual once. I think there was an allusion,
6 someone questioned in the protocol that is there a
7 situation where we would use another person, the same
8 person again if somebody dropped out of the study. And
9 I think if I recall correctly that happened once maybe
10 in the entire study, although I could be wrong about
11 that.

12 And in addition I think that the requirement,
13 if that ever had happened, is that that person, if they
14 are used again could not be used for a certain period
15 of time. They had to be spaced out in terms of time a
16 little bit. I mean it be several days to try to
17 minimize their affect. But never, so the bottom line
18 is we're not really interested in individuals being
19 measured close together in time.

20 So in general the other, the other monitoring
21 conditions are pretty much left up to the worker and
22 the attempt in here is to improve representativeness as
23 much as you can with a non-random design.

24 And what goes along with that, that second
25 bullet is pretty much saying, it follows along, it

1 permits the natural correlation among the factors to
2 sort of come out, with the exception of pounds per AI
3 handled, it's occurrence is going to be, is obviously
4 mandated but it's, but the correlation, anything that
5 happens to go along with it from a causal standpoint
6 will be, will still go along.

7 So if large pounds per AI are associated with
8 longer times, then longer times will tend to be spaced
9 out in such a way as the pounds per AI handled is.

10 But there are some and this is described in
11 Appendix B of the technical, there are situations where
12 some, what I call minor onsite diversification of other
13 miscellaneous conditions occur at the cluster level.
14 This is pretty much an informal attempt, not so much
15 formal as the other approaches were, but more of an
16 informal attempt to diversify. And you get an example
17 of maybe some equipment types, crops rates, the dates
18 of monitoring by location, things that sort of fall
19 within the purview of what would normally be used but
20 you have some sort of choices in the matter. So you
21 try to say, well, instead of these two people doing the
22 same thing they'll do something a little differently.

23 And the reason for this was to take what
24 looked to be a cluster affect that you see here in A, B
25 and C and spread things out just a little bit, force

1 them to be a little bit more diverse. Again there's a
2 difference between diversity and representativeness as
3 we freely admit here. We're trying to increase the
4 diversity, that does not necessarily mean it's more
5 representative because I think I talked to some folks
6 earlier that one could sample, get a sample of every
7 tie that's sold here in Washington, D.C., you get one
8 representative and you've got great diversity but that
9 doesn't represent the number of ties that are in use.
10 So it's really important to distinguish those two
11 concepts.

12 But diversity was seen as ours, as the
13 second, the second best thing from a random sample. It
14 was the next choice that we could have here.

15 As all the statisticians here know, and as
16 lot of people forget, that the, that when you do non-
17 random sampling that means that generalizing to the
18 target population becomes, is not a statistical
19 exercise anymore. It's a matter of, to be nice you say
20 subject matter expertise, you could also, some people
21 would say maybe faith is probably a better term to use
22 in that case. But nevertheless it's something that you
23 can't really, technically use statistics to do without
24 making further assumptions. And one of the assumptions
25 that is very common, maybe more common than it ought to

1 be, but it would be very common, is that this, the
2 purpose of this non-random sample can be approximated,
3 or can be approximated by a, some kind of a probability
4 sample from the target population. And if you make
5 that assumption, then of course you can go ahead and
6 use your statistics to make issues.

7 But you always need to keep in mind however
8 that even though this is common, that when you do that
9 you're running the risk that one runs is that the
10 probability statements that you make at best are only
11 approximate. And it's very difficult to judge that.
12 Maybe it's a function of subject matter expertise.

13 So going with non-random sampling isn't the
14 best choice but sometimes it's the only choice left
15 available to you.

16 Data adequacy and necessary sample sizes.
17 Assuming, we're going to assume that there is some sort
18 of a surrogate model that applies here just so we can
19 proceed forward. The AHETF program, in order to do
20 sample size there has to be some goals. I mean the
21 goal really shouldn't be just to collect data, to
22 develop data or whatever the terminology happens to be.
23 And then likewise to my knowledge there's no universal
24 optimal sample size that one could use, you know, be
25 that number 20, 30, 40, 50 or whatever. It, you really

1 need some, to establish some sort of purpose, some goal
2 and then maybe it's only approximate, maybe you're,
3 maybe it's based on assumptions but nevertheless you
4 then use that goal to establish some sort of sample
5 size that will address that goal.

6 And so we're going to do that. We, we're
7 doing this by setting what we're going to call these
8 benchmark objectives and benchmark objectives are
9 basically saying that these are objectives that we want
10 the data to accomplish for sure. If it doesn't it
11 doesn't mean that users of this data will have some
12 assurance that those, that the data used for those
13 purposes will meet certain objectives. It does not
14 mean that the users could only use the data for those
15 purposes, nor does it mean that the data are inadequate
16 for the other purposes. It just means that we cannot
17 specify as in a sense developers of a database
18 providing data, that every possible conceivable use of
19 the data by anybody, we can cover. Even if we could we
20 probably couldn't afford the sample sizes that it would
21 take to do that. But nevertheless it's very difficult
22 to do it so we have to settle on something, whether
23 it's the ones we're proposing or whether it's others
24 that the panel comes up with, you know, that's great.

25 But nevertheless we have to settle on

1 something so to get things started for this panel and
2 for the project we've proposed several things that we,
3 that get at things that, that get at goals, benchmark
4 goals which members of the Task Force and the Agency
5 seem to thing, certainly the Task Force for sure, seem
6 to feel were important or are objectives which the,
7 which were de facto, in other words, these are things
8 which people were using without actually explicitly
9 stating.

10 The two benchmark objectives that we're
11 talking about here are that the, and I'm going to
12 express them first in a general sense, that the first,
13 the primary objective is that selected measures of a
14 distribution, you know, some things like means
15 percentiles in sense is a feeling should be 'accurate',
16 and I'm putting that in quotes because accuracy here is
17 really going to depend on the surrogate distribution
18 assumption. But accurate to within K-fold when
19 exposures are normalized by amount of AI handled.

20 That last phrase might seem as though we're
21 saying that this database is designed to be a database
22 of normalized exposures and that's not the case. This
23 is going to be a database of exposures and many, many
24 factors, several of which are potential normalizing
25 factors. So it's not a database of normalized

1 exposure, it's a database of exposure and supporting
2 data.

3 However, we're saying that for the purposes
4 of sample sizes that the distribution of normalized
5 exposure will be, well we're trying to make it accurate
6 to a certain, we're going to have enough clusters and
7 numbers and individuals per cluster to achieve the
8 sample size, to achieve this objective.

9 It's also true however that it's going to
10 turn out that it doesn't really matter whether we're
11 talking about normalized exposure or some other measure
12 for this objective, as long as the probability model
13 that's used applies to some other measure, the results
14 will apply to that other measure too. So whether it's
15 just pure raw exposures or exposures normalized by time
16 or whatever.

17 The secondary objective in that suffix is
18 important. It's not second objective, it's secondary
19 objective. And it's in some sense subordinate. And
20 it's only to be met for some scenarios and those
21 scenarios are going to be those for which the amount of
22 AI handled is sufficiently broad so that it's possible
23 to do this, another sense, reasonably. And that is
24 that the users of the data should be able in some sense
25 distinguish between the complete proportionality case

1 and the complete independence case.

2 As you recall on the talk earlier today I
3 said that there would be, we were going to as a goal,
4 one of the goals was to provide some limited ability to
5 investigate pounds per AI handled. So in a sense we
6 might be guaranteeing this, not to say that users
7 cannot use it and be able to use it for more
8 complicated analyses, but we have to guarantee
9 something.

10 And to be useful these objectives really need
11 to be more precise. I'm not, I've only stated them in
12 a broad sense so they're not really very useful right
13 now. We have to give a little, a few little
14 preliminaries here. And one of the preliminaries is
15 that this is the model. Doctor Portier actually may
16 put a version of this up here later on when discussing
17 the variability with an additional variance component,
18 but this is the model we're sort of visualizing as a
19 surrogate for the purposes of sample size.

20 And what we're saying is that the normalized
21 exposure on a log scale is the log of the geometric
22 mean exposure plus a couple of random affects and those
23 random affects we're assuming are normal with the
24 variances, $V_{sub C}$, $V_{sub W}$, which is just a fancy
25 statistical way of saying that they're lognormally

1 distributed. And with the geometric mean of GM and the
2 geometric standard deviation, GSD, which is defined in
3 the terms of those variances as of here, as the back
4 transformed variance or standard deviation.

5 And the correlation between monitoring units,
6 monitoring events in the same cluster is described by
7 interclass correlation or ICC, where ICC is defined as
8 the ratio of these two, as the cluster variance divided
9 by the total variance.

10 You might wonder why I use the term ICC for
11 here and use the term RWW for the within worker
12 correlation. And mainly the reason was because people
13 got it confused when I talked about the interclass
14 correlation or ICC in one case and interclass
15 correlation for the other case and I find it just
16 simpler just to, just to use two different letters
17 because, even though I still confuse people I didn't
18 confuse them as often. And ICC is used for this case
19 because this is the first one done. And it was too
20 late to change it afterwards.

21 So determining the sample sizes, we've
22 already said what the model was. But in order to do
23 anything with this, to do anything useful we're going
24 to have need some reasonable values for the geometric
25 standard deviation and the interclass correlation. You

1 don't need in this case you're not going to need the
2 geometric mean because we're going to be talking about
3 relative variability so that's going to fall out. So
4 that's not really important in this case.

5 It is important when we analyze the data but
6 it's not going to be important for doing sample size.

7 We don't have values for that you might
8 think, so we examined some of the existing AHETF data
9 that's in the database now. These data consisted of
10 primarily the data that was acquired, purchased data,
11 and with some data then that was done prior to this,
12 the HSRB. And so there's a number data sets involved
13 in that as well.

14 In most cases these data had as you can,
15 here's the list of the scenarios for which we had data.
16 The one that says air blast is really one scenario, is
17 really sort of two manifestations of the same scenario
18 and one is with headgear and one's without headgear.
19 So that's really the same scenario there. And for the
20 purposes of this exercise I treat as one, because you
21 can see the results are very similar there in terms of
22 variability. Not in terms of the geometric mean by the
23 way. Without headgear it's a much lot higher because
24 of the head exposure.

25 The number of monitoring units in these

1 different scenarios that currently exist in the data
2 set I analyzed is give there in the table. And you can
3 see on the second column, those are the number of
4 clusters that are in the data. And you can see that a
5 few closed mixer/loader granule has one cluster and
6 hopper box seed treatment has one maybe. There's a,
7 it's a situation where we had two locations but we're
8 not really quite sure whether that's one or two
9 clusters. It's really, one falls on the, it falls on
10 the dividing line because it's separated spatially a
11 little, but the same individuals were used. Not the
12 monitoring units, the same personnel were being used in
13 both cases. There might be some association there so
14 for right now we're just calling it one.

15 And in that case the geometric standard
16 deviation we estimate, I'm going to just treat as
17 that's lower down from the estimate. In other words
18 the estimate, if I would, knew the cluster, knew it had
19 more than one cluster it would probably be higher
20 because I'm just measuring intra-cluster correlation
21 now.

22 Nevertheless these are the estimates of
23 geometric standard deviation. You have this data in
24 your, in the technical document, the second document
25 that was quoted, along with confidence intervals and

1 you also have the data for not just dermal but for
2 inhalation. So you've got a more complete data set in
3 the document. This is just shown up here for
4 illustrative purposes.

5 And you also have the interclass correlation
6 that was measured here so I used that model, that
7 variance component model that you saw a few slides back
8 on these data. And these are the results that we get.

9 One thing I wanted to point out, and it
10 should be very clear from the data you have in your, in
11 the report with a, from the table where the confidence
12 intervals are given, that the confidence intervals on
13 geometric standard deviation are certainly large. But
14 the confidence intervals on the interclass correlation
15 are ungodly large.

16 In many, for example I'm not sure of the
17 exact number but as I recall, I don't have it right in
18 front of me, but as I recall these ones in which the
19 interclass correlation is 0, I think the upper bound
20 could be up to around .6, in the vicinity of that. So
21 there's a large variation in interclass correlation.
22 In other words these kinds of measures are hard to
23 estimate, especially when you don't have a large number
24 of clusters. You need, as Dallas Johnson said earlier,
25 correctly so, it's not just the number of monitoring

1 units, it's the number of clusters that's important as
2 well to getting a good estimate there. And that's true
3 for anything else.

4 Nevertheless it looks as though these data
5 have quite a range. To give you a feel for these they
6 seem to range from say 5 right here for this one
7 scenario to I think the lowest was 2.5 for a dry
8 flowable mixer/loader, which is one of the better
9 studies. We got more complete data for that scenario
10 than perhaps many of the others. So it ranged from 2.5
11 to 5.

12 Well a geometric standard deviation of about
13 3 is about what, a coefficient variation of about 150,
14 something like that? Or maybe about an order of
15 magnitude variability, no, almost two orders of
16 magnitude variability. A geometric standard deviation
17 of 4 is about a 250 coefficient of variability, a 200%
18 coefficient of variability or about 2.5 orders of
19 magnitude. So in other words 95% of values range
20 within about 2.5 orders of magnitude. That's a pretty
21 substantial variability there.

22 If I look at the, if I look at the, not
23 saying that every one of those scenarios has the exact
24 same geometric standard deviation in interclass
25 correlation, but to get some sort of typical value to

1 use let's look at the summary statistics, the mean is
2 about 3.8, medium for geometric mean of maybe 3.3.,
3 this is for the geometric standard deviation. And if I
4 do a combined model of all the scenarios, allowing,
5 using, forcing the variation components to be the same,
6 but the geometric means or the means on the log scale
7 to be different, then you get something like 3.8 as
8 summary statistics. So think of that as just a
9 glorified summary.

10 And the ICCs are a tad, somewhere between 2.5
11 to, I'm sorry, .25 to 3. So if I were going to pick a
12 number, rounding it off suitably to use for maybe
13 looking at sample sizes, at least as a first pass, it
14 seems like something like 4 and 0.3 might be
15 reasonable. Especially since I think if you look at,
16 you have the table for inhalation which gives summary
17 statistics a tad higher than that, maybe just as far on
18 the upper side, it seems like 4 and 3 might be
19 something that's useable for both. So I picked 4 and
20 0.3 as something that's, something to use at least as a
21 start to get estimates for, for sample size or
22 investigating these goals.

23 Now we're ready to look at the goals a little
24 more precisely. I'll narrow this down a bit by saying
25 we know that the number of clusters and monitoring

1 units per cluster and they should be sufficient so that
2 these estimates of the geometric, arithmetic mean in
3 the 95th percentile from the surrogate logarithm of
4 distribution with specific, you know, yada, yada, yada
5 geometric standard deviation and ICC should be within
6 K-fold of the true values in this 95th percentile.

7 Now I'm putting a little bit more precision
8 on this just to give us something that we can work
9 with.

10 The reason I'm picking the geometric, the
11 arithmetic mean and 95th percentile is mainly because
12 the geometric mean is easy to measure and there's
13 actually an analytical solution for that. I don't have
14 to resort to simulation to work with that. Arithmetic
15 mean and 95th percentiles are very, are statistics in
16 the distribution that are quite of interest in the
17 regulatory arena. So those seem to be reasonable
18 statistics to focus on.

19 K-fold, the, it's not going to take rocket
20 scientist to figure out that the more stringent
21 requirements you put on K, the larger the sample size
22 is going to be and the more relaxed it is, the lower
23 the sample size is going to be. And it's very
24 difficult to figure out, to ask the question, what kind
25 of error or relative variability then to tolerate on

1 the results? And it's very difficult to get that.

2 Through numerous with people at the AHETF and
3 getting a feel by saying things like, well, if you got
4 a result like this, how far off would it have to be
5 before you'd say things are useless? So using
6 questions and answers like we sort of honed in on
7 something that 3 at least is a start. It might be
8 something that seems kind of reasonable.

9 Much more than that we're starting to say,
10 well, you know, I'm not so sure that it's giving us
11 very useful information and you know what's going to
12 happen is much more precise, much more lower than that.

13 So as an example, not to say this is hard,
14 this isn't a hard and fast rule and it certainly is not
15 going to necessarily be true for every scenario, but
16 just as, for an example so that we can get something to
17 work with, let's just work with 3 and that's an example
18 I used in the document. And I want to just emphasize
19 that that should be treated as an illustration, not as
20 the agent, not as the Task Force's recommendation that
21 that's what should be used. This is a, we're trying to
22 come up with something, a process as opposed to
23 necessarily a specific number. And this is what we saw
24 as an approach to address the process.

25 Nevertheless, 3 is what we'll use as an

1 example.

2 You can go through and do, and I have
3 described the simulations and I think actually the
4 panel has received the SASS programs that were used,
5 either ours or the Agency's, I'm not sure which version
6 you got. But the Agency did a validation in a sense or
7 let's say, I mean validation is too strong a word, they
8 tried to reproduce the results themselves and so I'm
9 assuming they sent mine, but if they did you call tell
10 because I'll have my name on it somewhere.

11 In any event, you can use the simulations and
12 as I said the, in some cases the geometric, for the
13 geometric mean you don't need simulation to address the
14 result. But it was just as easy to include it for
15 generalizing, for generalizability.

16 But nevertheless what we do is we generate,
17 we take the number of clusters, say 5 in this example
18 and the number of monitoring units per cluster, in this
19 case it's 5 as well. We look at the geometric standard
20 deviation and the interclass correlation, generate data
21 that correspond to that model, then calculate the
22 statistics of interest. And there are many different
23 ways of calculating them but in the, and I think I
24 presented at least one way here, calculate an estimate
25 of geometric mean, the arithmetic mean, 95th

1 percentile, look to see how far off they are from the
2 values you started with and from the lognormal
3 distribution for the 'true values'.

4 And look at that in terms of a ratio and
5 that's what we call the, and the 95th percentile, I'm
6 sorry, the 95% bounds, the 97.5% and the 2.5% whichever
7 bound is bigger, that's basically what we're using for
8 this and looking at the relative variability. So in
9 other words what we're seeing is an example of the
10 geometric mean is that it says 2.2., that should be
11 interpreted as saying the error in the geometric mean
12 is going to be less than or equal to 2.2 with a
13 probability of 95% apart from simulation error. And I
14 think in this case I used 10,000 replicate simulations
15 in this instance.

16 And these are the results we get and what I'm
17 showing you is the result of several different
18 simulations. I'm picking the one here that gave a
19 result that was, that seemed to be close to a
20 threefold, it seemed to be that those boundaries at
21 least were within threefold. And it's always going to
22 be the case that the higher percentiles are going to be
23 more uncertain than the lower percentiles, I'm sorry,
24 that the percentile is more towards the center.

25 This is a lognormal distribution so the

1 arithmetic mean is often around in this case the 70th
2 or 80th percentile anyway. So an arithmetic mean in a
3 lognormal distribution is up in the higher percentile
4 so it's going to also tend to have, and that depends on
5 how the, what the geometric standard deviation is. But
6 it's going to be very close in terms of the geometric
7 mean and the precision will be higher as well.

8 So these last two parameters, 95th percentile
9 and arithmetic mean are driving the results. If you go
10 to the 99th percentile or 99.999 or whatever you want
11 to go, the error is even bigger.

12 So this is an example. We, I looked at many
13 different examples, you've got those example I think,
14 both from sort of a sensitivity analysis approach and
15 also looking at some of their values in the document.
16 I don't think it's in the document but just if you're
17 curious, with this scheme if you wanted to go down to
18 say 2, for twofold, instead of having numbers like, and
19 let's just say 5 monitoring units per cluster just to
20 stabilize it, you'd be getting about, you'd have to
21 have 12 clusters with 5 per cluster so that would be
22 in, that would be like 60 monitoring units.

23 So you'd more than double the sample size to
24 go from 3 to 2. To go to, from, to get down to say
25 1.5, a relative error of 1.5, it's like saying the

1 estimates up there are plus or minus 50%. I think as I
2 recall, I'm thinking it's around 200 total
3 observations. So whatever that would be 40, I think 40
4 clusters times 5. Is that right? Yeah, or something
5 like that, 40 or 50, it's very, it's close to 150 or
6 200 so it's a, the sample size, it's not surprising,
7 the sample size is, as Doctor Heeringa mentioned
8 earlier when talking about the interclass correlations,
9 the sample sizes are going to start going up like the,
10 go up by a factor of 4 every time something else goes
11 by a factor of 2. It just, it tends to get worse and
12 worse as you get tighter and tighter.

13 You're never going to get anywhere near the
14 kind of precision or accuracy you might expect of
15 studies, like plus or minus 10%. I mean that, if
16 you're wishing to have errors plus or minus 10% or 20%
17 or 30% I think it's wishful thinking. Not with this
18 kind of variability.

19 It may be that if you, as someone suggested,
20 if you nail the scenarios down or some scenarios down
21 to real, real narrow and focus on scenarios like that,
22 that if a lot of the variability tends to decrease, and
23 I expect that there would be some, then you might gain
24 this. But just keep in mind that the, that even for a
25 scenario or even within a study oftentimes we've seen,

1 I think it was the, I can't think of which one it was
2 now, the study that's on the very bottom, let me skip
3 back here, there we go, open pour mixer/loader, I think
4 that the, that there was one study in which the
5 individuals were applying separately, or not applying,
6 this is a mixer/loading, were doing it separately, they
7 were scattered out over several days but it was all in
8 the same study so you've got a cluster. Within that
9 one cluster there were three orders of magnitude
10 variability.

11 So we're talking about, so if I narrowed that
12 scenario down to that single, that single cluster, that
13 one location, that one, I think it would have had to
14 France, I'm not really sure about that but it was
15 single, it was a purchased study, a single, a single
16 cluster that was done over the course of say two or
17 three weeks, you had three orders of magnitude
18 variability in terms of the exposure.

19 So maybe the, maybe that's an exception to
20 the rule but it seems like it might be not as obvious
21 that cutting down the scenarios is necessarily going to
22 cut down the variability always.

23 Did I do something wrong here? Oh, that's
24 great, that was a feature I think, not a bug.

25 The, anyway overall the scenarios seem to me

1 anyway that the accuracy, and you'll see this, I'm not
2 going over it but the accuracy is, the information is
3 in your document, that the accuracy seemed to be
4 influenced more by the number of clusters than the
5 monitoring units per cluster. That's not, it should be
6 not a surprise, it's the same issue you saw with the
7 interclass correlation for within worker and between
8 worker. If there's a correlation within a cluster then
9 it's to your benefit to take more clusters, not waste
10 your effort to take more individuals per cluster.

11 The only reason, and somebody over here
12 mentioned it earlier, that it's cost considerations
13 oftentimes while you do cluster sampling. Cluster
14 sampling, it's sort of like they say democracy is the
15 worst form of government except for all others.
16 Cluster sampling sometimes is bad but it may be the
17 only choice you have in some cases.

18 Give a large variation exposure this
19 geometric standard deviation of 4 or 3 or even 5, there
20 are pretty much practical limits to how much the
21 accuracy is going to be increased. I mean like I said
22 before, going down to 10% is wishful thinking.

23 In this example we gave here a threefold
24 accuracy could be achieved with 5 clusters and 5
25 monitoring units per cluster as long as the surrogate

1 model holds. With that caveat there.

2 And the result is not exceptionally sensitive
3 to small changes in the geometric mean in the ICC
4 unless they both happen to vary, increase in the same
5 direction or you underestimate them in the same
6 direction.

7 And just to say again that we as the Task
8 Force are not saying that even if we pick a value like
9 threefold we would necessarily use that for every
10 scenario. So whatever value is picked is not
11 necessarily going to be used in every scenario. It
12 might be that the variation we know for, in some cases
13 the variation in some scenarios is lower than others.
14 Not just due to random variability but we have some
15 evidence other than just that from just sample data,
16 it's something a little more stronger perhaps.

17 In that case if there's lower, I mean it's
18 not, it doesn't take rocket science to tell you that if
19 the variability is lower you can use a smaller sample
20 size, if the variability is higher you need a larger
21 sample size.

22 Increased accuracy is desired if that's the
23 case. If you need twofold in some cases and say
24 fourfold in others, an example given might be that if
25 it's a very important and high risk scenario in some

1 sense you might want more accuracy, especially in the
2 upper end. If it's a scenario where the exposures
3 typically are low it might not be quite as important to
4 have the same level of accuracy. That's really
5 something that's not for a statistician or for me to
6 decide. It's really something that people who use the
7 data or are planning to generate the data need to make
8 the decisions on.

9 And I guess because, this is just an artifact
10 here, but the purchased data in the scenario, the
11 purchased data available, some of those have very, very
12 large numbers of monitoring units per cluster. And in
13 that case, if you have say 16 monitoring units per
14 cluster or 10, then those don't contribute too much to
15 the cluster, you going to still going to need say, if I
16 say that 5 and 5 are needed I'm still going to have to
17 have pretty much 5 for all the others besides that one.
18 Because you don't really, you don't gain a whole lot of
19 information by that 16, that 16 doesn't give three
20 times as much information as a cluster of 5.

21 Okay, closing down this, the surrogate, let's
22 look at the secondary objective real quickly. The
23 secondary objective, I can sort of rearrange and
24 redefine the surrogate sampling model in terms of the
25 log exposure is equal to some linear function of the

1 amount of AI handled and it also has those same two
2 variance components that we talked about before.

3 And expressed in this form, we've already
4 talked about this many times so it shouldn't be too
5 different from what you've already seen, that if the
6 slope is equal to 1 then exposure is proportional to
7 amount of AI handled. If the slope is equal to 0 then
8 the whole turn with the log AI drops out and you've
9 basically a simple variance component model for
10 exposure and pounds per AI handled is unrelated.

11 So there are two extremes. Granted, there
12 are many things in between and things that aren't even
13 described by this model. But nevertheless we can
14 reduce this secondary objective to a situation where
15 we're just testing whether the slope is equal to 1
16 or 0.

17 So to make this objective more specific I'm
18 going to say that for scenarios with at least a 10x
19 practical range of AI handled, and maybe that should be
20 even bigger than 10x given the variability that we see
21 in normal I think Doctor Pependorf mentioned that
22 earlier that we should be, might be wanting to make
23 that even bigger, it probably needs to be bigger. Even
24 where the data should be adequate and I'm going to say
25 sort of the power to reject the hypothesis that this

1 slope is 0 and the slope really is 1 is at least 80%
2 and symmetrically you can reverse that in this case
3 under certain assumptions and say that is also the same
4 as saying that you have the same power to test the
5 other way.

6 In other words you're going to reject the
7 slope being 1 when it really is 0. That clearly does
8 not take all possibly hypotheses you can test but it
9 does at least get at something.

10 So what you need is a surrogate cluster
11 sampling model, we already mentioned that, that's in
12 the previous slide, you need reasonable values for the
13 residual, geometric standard deviation and the ICC. I
14 think the values of 4 and 0.3 are probably reasonable
15 for this as well.

16 The power in this case however really depends
17 also on how those amounts of AI handled are allocated
18 among the clusters, both what the levels are and how
19 they are allocated. And that's kind of tricky.

20 We've already said that we're trying to
21 spread the AI levels out sort of logarithmically and I
22 think if we assume that that's the case then we've
23 addressed the first part. The second part is how are
24 we going to allocate those AI levels, I'm sorry, the
25 amount of AI handled out among the clusters becomes

1 kind of problematic.

2 What I've done in this example is present two
3 alternatives. One is which, most of the AI values are
4 in the, the AI values are maximum overlap, that's the
5 bottom example there. So we achieve maximum overlap
6 within each, each individual cluster has a wide, the
7 widest range possible of amount of AI handled and given
8 the spacing. And the other cluster has the, those are
9 just the opposite, it scrunches as many of the AI
10 levels and minimizes or allows no overlap at all.

11 What you would expect in this situation if
12 there's a cluster affects is that the top one would be
13 worse because now the cluster affects are being
14 confounded with the affects of amount of AI handled.

15 Whereas in the bottom case you would expect
16 that to be a bit better because now the cluster affects
17 are sort of like blocks in a way and your, it's not
18 contributing to the additional variability of that
19 estimation of the slop.

20 I'm not going to go over all of the different
21 things that we've examined but just to give an example,
22 you also use simulation to address this and basically
23 this means joining the data under one of those two
24 assumptions and then plugging the results, the
25 simulated results into a mixed model for variance

1 components, testing for the slope, being from 0 or 1,
2 depending on which way you want to go and look to see
3 what proportion of time that actually is rejected.
4 That's your power.

5 So for example on the second line down where
6 it says 8x, if the range in the amount of AI handled is
7 eightfold, then in that case of minimum overlap between
8 the two, within the clusters, only 37% of the time
9 would you reject the hypothesis when it's false.

10 In the case of the maximum overlap you do it
11 82% of the time. Again the caveat being that there's
12 simulation error, whatever is associated with that
13 which is rather small.

14 So you can see that the intuitive assumption
15 is true that the, that that, when you have maximum
16 overlap between the clusters you're actually doing
17 better in terms of this association.

18 You can bump the power up by increasing the
19 pounds of AI handled range. So when you're up around
20 50x you can see that you're almost at the 80% power.
21 And certainly at 100x. So that works and it's also
22 shown in the simulation that you've got in your report,
23 that you can increase the number of clusters to
24 compensate for this and to some extent even the number
25 of individuals per cluster, but that's probably

1 inefficient.

2 But in that second case there the only
3 solution is to use, really to use more clusters because
4 in that case what you don't have is, you don't have,
5 say if you have 20, if you have 25 observations in 5
6 clusters you don't have 25 observations, you've got
7 sort of 5 fuzzy observations there. And you need more
8 of those fuzzy observations in order to compensate for
9 that.

10 So there is, that's the kind of issues that
11 you have to work with.

12 In examining several simulations it seemed to
13 me is that if we're going to assume that things are
14 logarithmically spaced and the amount of AI handled is
15 at or greater than an order of magnitude and there is
16 some strong overlap between the AI levels and the
17 clusters, that it seemed that in this specific example
18 anyway, that when you met the first objective, the
19 second came along pretty much for free.

20 That may not be true in all cases but it's
21 certainly something that needs to be, would have to be
22 investigated. But in this example that seemed to be
23 what happened.

24 Okay, only a few more slides and we're home
25 free. You are, I'm not.

1 The statistical analysis of the data, I just
2 want to say, and this is something that's very easy to
3 be confusing here because it's, I just want to remind
4 you that the Task Force, our purpose isn't to analyze
5 the data really. Our purpose is to generate the data
6 that others are going to analyze. And so we're not
7 really here in a conventional experimental study that
8 we're going to take the data, analyze it, write a
9 report, write a paper or two and get tenure or
10 whatever.

11 What we're going to do is provide data for
12 others to analyze so, however what we want to do is we
13 want to make sure that others have data that is going
14 to be useful to them but we cannot anticipate every
15 kind of analyses that's done and that's why the generic
16 database is going to provide many different features
17 for people to do things on their own, something that
18 may not even have been anticipated. You can, obviously
19 you're able to query the data, pull out data based on
20 any of these factors that are in the database.

21 You're going to be able to calculate exposure
22 pretty much normalized or transformed pretty much in
23 many, many different ways. And if the database
24 software itself does not provide the analyses that you
25 need to do, you need something more specialized, all

1 the data can be easily exported I think as I recall to,
2 probably I think into an Excel format which then can be
3 put into some other format. Any, most any data, any
4 statistical analysis program will handle that.

5 So users of the database can do pretty much
6 anything they want. Our analysis is pretty much going
7 to be limited to attempting to verify that whatever
8 requirements that we say we meet, we try to make an
9 attempt to verify that level of adequacy. And also to
10 provide some guidance to users regarding proper use of
11 the data. For example, the issues of clusters and
12 things like that to provide as much, it's mostly like
13 documentation from a statistical point of view.

14 Those, that information is going to be
15 provided in something called a scenario monograph which
16 also will include many, many other pieces of
17 information and I think that's described in the
18 technical document that was provided. Not the one on
19 the sample size but the other one I think in Section 9
20 or 10 or something like that.

21 The main focus of our analysis is basically
22 going to be things like confidence intervals for the
23 distribution parameter, the parameter estimates, some
24 post hoc power information, that sort of stuff.

25 And I wanted to say that if the, if it turns

1 out that the data are somehow grossly inadequate from
2 what the goals were, the Task Force is certainly going
3 to consider augmenting the data with additional
4 clusters. You almost have to talk about additional
5 clusters because you can't go back into a cluster once
6 you've already done it. A new study is going to be a
7 new cluster.

8 So certainly there's going to be some
9 guarantee that the, whatever adequacy requirements can
10 be set, no matter how we do it, are either met or
11 determined not to be a problem, one of those two
12 things.

13 But I guess I should say, and this is where
14 the confusion comes, when you're looking at some of
15 these, and this is what people I think thought we were,
16 our purpose of a database was to generate, to basically
17 provide estimates of normalized exposure. It turns out
18 that in order to get the confidence limits for the
19 parameters of the normalized distribution, we're going
20 to have to calculate the parameters of the normal,
21 estimate the parameters of the normalized distribution
22 and do confidence intervals.

23 And so as part of testing for the adequacy
24 we're also going to be in effect making that
25 calculation. So we'll be providing some descriptive

1 information, some estimates of the distribution of
2 normalized exposure just because we need it in order to
3 do other things.

4 And in addition in doing like I say, a power
5 comparison for the regression, the test of effective
6 amount of AI handled, they almost have to do in order
7 to get some sort of estimates you almost have to do the
8 regression in the process so you end up getting those
9 results anyway. To what form we'll actually put those
10 in the scenario monographs hasn't really been decided
11 yet.

12 So this is where the confusion comes out, it
13 seems as though people sometimes are mistaken that we,
14 this is what our purpose of the data, our purpose is to
15 somehow collect data so that we can analyze and provide
16 these estimates. Our purpose is to collect data so
17 that others can do things with it but we also want to
18 establish some sort of benchmark.

19 And I guess in addition as I said we'll
20 provide information like, things like degree of
21 confounding, variance factors, and description of the
22 clustering so that people will know what the clusters
23 were and this sort of information so that users who
24 really are sophisticated can factor these things in.

25 And so in summary then let me just say that

1 the, we started off saying that we're talking about our
2 purpose of sample and monitoring units with certain
3 objectives that we're sort of thinking about right now,
4 and proposing actually about using.

5 Threefold, there's nothing magical about that,
6 that seems to be something that's been tossed around
7 alot.

8 It that level is there it sort of translates
9 into 5 clusters and 5 monitoring units per cluster,
10 given the data, the assumptions we used in the sample
11 size estimation.

12 And just to say again that the AHETF
13 statistical analyses are going to be limited to really
14 focused on evaluating the adequacy, not doing analyses
15 for our own purpose.

16 Thank you very much.

17 DR. HEERINGA: Thank you very much Doctor
18 Holden for that presentation. A lot of material again,
19 I think very nicely organized, systematically
20 presented.

21 I want to turn to the panel now. I think
22 certainly we would like to cover some initial questions
23 of clarifications on this presentation and some of the
24 sample size issues. Doctor MacDonald.

25 DR. MACDONALD: Yeah, there were two

1 numbers that you've used that I don't see a
2 justification for yet. Maybe you could explain where
3 they came from. First of all the 5 MUs per cluster and
4 secondly the 95th percentile of exposure is the highest
5 you've considered and both of those choices have
6 real implications for the sample size.

7 Can you explain where those two numbers came
8 from please?

9 DR. HOLDEN: Yeah, the 95th percentile is
10 one where there seems to be an interest in the Task
11 Force. And again these are, I must say these are
12 examples. So there's nothing that says that these have
13 to be, and we're not necessarily, you know, wedded to
14 these numbers. But the justification for the 95th
15 percentile is these happen to be numbers in which, at
16 least that I was informed, were very, very commonly
17 used regulatory estimates from the distribution. These
18 were used in many cases and the 95th percentile and the
19 arithmetic mean, the geometric mean just came along for
20 free so that's just provided.

21 Granted, I've heard that there are other, I'm
22 sure there are other people who have used like the 99th
23 percentile, like food consumption and this sort of
24 stuff like that. And so those issues, and we knew that
25 the higher one, percentiles you use, the relative

1 accuracy gets worse and worse and worse. The
2 99.99999th percentile is a heck of a lot worse than
3 99th.

4 And so, and so those, so there's a point at
5 which we stop. We just picked these saying that we're
6 going to guarantee something and those are the two
7 numbers that we say we're going to guarantee.

8 If it turns out that there is a very great
9 need to have adequacy for a much higher percentile,
10 then we'll use that number.

11 So, assuming that this process is used, not
12 some other process but if that process is used then a
13 higher percentile will be used as a benchmark and the
14 now the relative accuracy, it may be that given
15 resources and needs, it may be that the relative
16 accuracy required for the 99th percentile might be less
17 stringent than for the 95th let's say or the 90th or the
18 75th given certain considerations.

19 Because the sample size implication is such
20 that we aren't going to do, let's say, I'm just making
21 this up, let's say that it's impossible to do the study
22 or cut back on a number of scenarios, you know, there's
23 cost considerations, if required that the 99th
24 percentile be accurate within 50%. In which case
25 something's going to have to give, it's going to be the

1 number of scenarios, the number of, how scenario is
2 defined, the number of replicates or something. Or
3 it's going to be, what's going to give is the precision
4 requirements.

5 But what we do want to ensure, I think it's
6 really important that whatever requirement is establish
7 and however it's done, we don't want to say that we're
8 going to generate something that's going to have and
9 objective that when push comes to shove people say, I'm
10 really not happy with.

11 Because if it, you know, we don't want to
12 just to do just because we can do it. It doesn't seem
13 to make a lot of sense to me at least. So, so whatever
14 happens, so that's the 95th percentile.

15 I hope that's an answer. Maybe not the
16 answer you wanted but it's an answer.

17 The other question was the

18 DR. MACDONALD: The 5 per cluster.

19 DR. HOLDEN: Oh, 5 per cluster. I did
20 look, and there are other choices and I think what's,
21 what happens is that that again was examples and I
22 didn't say, I didn't mean to imply that 5 per cluster
23 oh, no, a target of around 5 per cluster appeared to
24 meet the benchmark requirements.

25 I'm not saying that there aren't other

1 configurations that are going to also meet the
2 benchmark requirements. In fact, using, I think an
3 example I gave you could use fewer, fewer numbers per
4 clusters, fewer monitoring units per cluster with a
5 large number of clusters and actually come out with
6 actually a smaller total sample size.

7 What's happens is that there's cost
8 implications of those and before a decision, a final
9 decision will be made I think that might have to, a
10 balance might have to be established between the cost.
11 Now the cost, the cost of, given the same number of
12 observations, putting more into more clusters is going
13 to give you, changing the balance to more clusters
14 gives you a better precision, at least in this case.
15 But also it might be more costly.

16 And so there's a balance, I think, you're the
17 one who mentioned, earlier the clusters, the effect of
18 doing cluster sampling? I think it was, wasn't it?

19 DR. MACDONALD: Yeah, yes and that

20 DR. HOLDEN: Right and this is the issue
21 that came up

22 DR. MACDONALD: that's a fairly

23 DR. HOLDEN: in the clustering sampling.

24 DR. MACDONALD: there's fairly we known
25 formulas for working through that.

1 DR. HOLDEN: Yes, that's right. That's
2 right. Well, there are cost allocation formulas for
3 doing that that can be used. And if those formulas
4 don't work it may be that the specific, and I'm really
5 a fan of not using a conventional sample size formula.

6 If the formula that you use is based on some
7 end point that you're not interested in I'd much rather
8 use simulation say for end points you are interested
9 in, than an exact or quick calculation for one you're
10 not.

11 But nevertheless the principle is still the
12 same, the allocation of cost principles are the same.
13 You're right, absolutely right.

14 DR. HEERINGA: Doctor Holden, someone
15 raised the question earlier and I'm interested too.

16 I know you can't put specific or exact costs
17 on the different components of these data collection
18 activities, but in general, and I think the big
19 question is, you know, is the cost in getting the data
20 collection teams to the location or is the cost in the
21 assays of the actual dosimeters?

22 What is sort of the relative order of
23 magnitude? I mean is the cost in the analytic
24 component of that? Is it five times the cost of flying
25 somebody to the Central Valley to oversee this

1 administration and pick up these and bag these clothes?

2 DR. CANEZ: This is Victor Canez. I'd say
3 it varies, but among all the monitoring units we've
4 done we look at 5 monitoring units in one cluster as
5 kind of the economic threshold that we want to go out
6 there.

7 And it turns out I'd say over all the
8 monitoring units we've done, it averages to about
9 \$18,000 per monitoring unit. And those are divided up
10 into, obviously if we do more monitoring units at one
11 location it comes up cheaper.

12 The analytical costs are pretty much the same
13 but there is some time to set up to go there, find the
14 workers, find the sites, do all that up front
15 coordination. And then there is some time and cost
16 involved in camping out there. If you have rain you're
17 out there longer. And so depending on that period that
18 could impact it also.

19 And so that's pretty much how they're divided
20 up into those three areas, the initial cost, the study
21 conduct and the analytical costs.

22 DR. HEERINGA: And roughly what ratio, did
23 you have any sense of what those, say if you had to go
24 is it

25 DR. CANEZ: I'd say the analytical costs

1 are a little bit under 50%.

2 DR. HEERINGA: Very good. And the others
3 we can, that's really the main element. And I think
4 your own sense too that, you know, your experience,
5 you've sort of done this cost optimization in your head
6 if not on paper.

7 The one question that I have is that if you
8 design for studies, or your recommended protocol is for
9 5 measurement units per cluster, does that limit the
10 type of applications that you might consider?

11 Let's say somebody has 40 acres of orchards
12 and that's what they have and that might well be a good
13 half day or full day's work for one person, or it might
14 be two half days for two people, but it certainly
15 wouldn't , you wouldn't want to necessarily split it
16 up.

17 Do you have to look for large scale
18 operations in order to make this work?

19 DR. CANEZ: It depends a lot on the
20 scenario we're looking at. And with some scenarios
21 where we're looking at let's say orchard, for the
22 example you used we're looking for open cab or orchard
23 applications, those are generally, in some areas
24 they're smaller farms and so you might have only 40
25 acres. In cases like that we're going to do, we're

1 going to go to one, go to a place and on one day we may
2 use that all 40 acres. The next day we may pack up and
3 go to another location where there's another farmer
4 with another 40 acres and those sorts of things.

5 If we're lucky we find two farmers in one
6 place and each of them have 40 acres.

7 So it just varies on the situation, the
8 equipment, the number of acreage we need, depending on
9 the application rate. So it just, it's one of those
10 coordination efforts that has to be done before we get
11 to the place.

12 DR. HEERINGA: Yeah, but getting back to
13 that, the reason I raised that is I was getting back to
14 Doctor Landers' concern of, you know, small operators,
15 association with equipment types, et cetera.

16 The reasons I asked was to think, you know,
17 is there any sort of prejudice in this choice against
18 going to smaller operations?

19 And what you're saying is that if you looked
20 at say small here, we're not looking at Ma and Pa
21 orchards but, you know, say 40 acres that you might
22 find multiple locations in the same physical vicinity
23 to distribute your observations in.

24 DR. CANEZ: Yes, you're right. In some
25 places there's corporate farms that have many acres and

1 they have many 40 acre blocks.

2 When you start looking at different types of
3 equipment, closed cab ground boom application, those
4 are usually large operations, these guys move through
5 the fields and you'll have farms that'll, that have all
6 the acreage you need.

7 But if you go to an open cab ground boom
8 application you're going to be mostly looking at small
9 farmers.

10 So it depends on the operation. But you will
11 find some small farmers with closed cabs so, you know,
12 you can fill those gaps in also.

13 DR. HEERINGA: But it sounds like the
14 scale bias that I was concerned about is really pretty
15 much taken into account when you break out the
16 different scenarios?

17 DR. CANEZ: Yes, yes.

18 DR. HEERINGA: Thank you. Members of the
19 panel, Doctor Johnson.

20 DR. JOHNSON: Thank you. Can we put slide
21 up there for a second?

22 The one question I had on this particular
23 slide is that in the monitoring units there that are
24 within each cluster, are those unique individuals or
25 are there some individuals that have been measured more

1 than once?

2 DR. HOLDEN: It's a good question. For
3 the most part the, there's the combination of studies
4 there. There's studies that were acquired previously
5 and then there's studies that were, new studies that
6 the Task Force has augmented to that, that were done
7 before the HSRB.

8 And the ones the Task Force did, every one is
9 an individual study. The ones that were acquired,
10 there are a few studies and I, the only one I know for
11 sure, the aerial one, I know that some of those in the
12 aerial application, and Victor probably knows this much
13 better than I do, I'll let him comment in detail, but i
14 know those were repeat, some of those were repeated,
15 the same individual repeated.

16 Although I think almost all always, not
17 always, not almost always, in many case there were like
18 separate days but I think there is actually was one
19 case inthe aerial where they were two per day with the
20 same individual, he did two per day.

21 And so that's, but that's something that
22 we're avoiding in our, in the data we are collecting.
23 That's something we don't want at all.

24 DR. JOHNSON: Right. The second question
25 on that same table, you'd think after as many years as

1 I've been involved with analyzing data, I have to admit
2 I never looked at much in terms of where I had to look
3 at geometric means. I always made things not so messy
4 that I couldn't call it normal.

5 And so if I had lognormal data I'd generally
6 log it and then think of it in terms of normal stuff
7 anyway and getting my confidence intervals and
8 everything and then I'd just exponentiate the end
9 points to get back to the raw units on which the data
10 were analyzed.

11 So I'm having, what I want to ask you I guess
12 is if I think about this then, when I look at this
13 geometric standard deviation, mostly I'm thinking about
14 when I look at a regular standard deviation I sort of
15 think of a mean plus or minus so many standard
16 deviations.

17 So here when I look at a geometric mean and I
18 don't really want to add and subtract the geometric
19 standard deviation, the I want to divide and multiply
20 by it, is that right?

21 DR. HOLDEN: Yeah, that's right. I think
22 I'm going to have to run it myself but the geometric
23 standard deviation, you could think of it as,
24 oftentimes when people use the geometric mean, when you
25 multiply it times the geometric standard deviation, and

1 that gives you, the sort of equivalent of one standard
2 geometric deviation above the mean, if you do it with
3 the log scale.

4 Or then you divide by it and you get, so if
5 you take those two numbers, the geometric mean times
6 the geometric standard deviation and take the log of
7 it, and you take the, or you take the geometric
8 standard deviation, I'm sorry, the geometric mean
9 divided by the standard, geometric standard deviation,
10 take a log of that, that would be equivalent on the log
11 scale to the mean plus or minus one standard deviation.

12 And likewise I think if you, what people
13 oftentimes do is take the geometric standard deviation
14 and take it to the, to some normal quantile and that
15 gives you a sort of confidence balance on it.

16 But yet you put it in the exponent I think as
17 I, if I recall correctly. Is that right?

18 DR. PORTIER: Just take a log, do the
19 standard plus or minus and then re-exponentiate it and
20 you've got the

21 DR. HOLDEN: Yeah, that's what I do too, I
22 was telling you that other people do it. Yeah, I'm no
23 fool.

24 DR. JOHNSON: That's what I say, I'm an
25 old dog.

1 But then the other thing I was trying to do
2 is then try to figure out what the meaning of this K-
3 fold measure of accuracy is.

4 And so the K-fold would be like if I had a
5 geometric standard deviation of 4 then a K-fold would
6 be, well, if I take the log of the, of 3, I get 1.1
7 approximately so a K-fold, I guess a K-fold measure of
8 accuracy would be equivalent to being within 1.1 units
9 on the log scale. Is that right?

10 DR. HOLDEN: I'm not

11 DR. PORTIER: Sorry.

12 DR. HOLDEN: That's fine.

13 DR. PORTIER: A 3 is pretty tight, right,
14 on a log scale? That's a

15 DR. HOLDEN: Yeah, so it's about a .7
16 standard deviation.

17 DR. PORTIER: I have a question.

18 DR. HEERINGA: Okay, Doctor Portier.

19 DR. PORTIER: I was looking at the same
20 graph, you know. One of the points that I see here is
21 that your GSDs and ICCs really are estimates, right?
22 Based on the data.

23 And so you don't have it on this chart but on
24 Table 2 in the document that we have you have upper
25 and, you have confidence intervals, upper and lower

1 bound

2 DR. HOLDEN: That's correct.

3 DR. PORTIER: and, you know, normal risk
4 assessors would say, well, I'm not going to base my
5 sample size on this estimate, I'm going to use the
6 upper 95% CI to base my sample size on because that's
7 my more conservative mean concentration level.

8 And I was trying to figure out for the ICC
9 whether I want the lower bound or the upper bound, but
10 I think I want the upper bound to be more conservative.

11 In which case your 5.5 becomes something more
12 like a 7 or a 10.3, right?

13 DR. HOLDEN: Oh yeah, absolutely,
14 absolutely. Yeah, if you take the worst case,
15 basically saying the data I have, what's the most,
16 what's the highest it possibly could be, you know, you
17 could think that way.

18 And basically if I design my study around
19 that, then I can guarantee you that no study would get
20 done in that case.

21 DR. PORTIER: I'm just trying to get back
22 to the

23 DR. HOLDEN: Yeah.

24 DR. PORTIER: 30.

25 DR. HOLDEN: Yeah.

1 DR. PORTIER: That's we had two days ago,
2 right? So I'm saying

3 DR. HOLDEN: Yeah, that's right, that's
4 right.

5 DR. PORTIER: 30. So where did that
6 come from?

7 DR. HOLDEN: It may turn out to be 30 but
8 I think there ought to be a reason for it.

9 DR. PORTIER: Yeah.

10 DR. HEERINGA: Doctor Johnson and then
11 Cynthia Hines.

12 DR. JOHNSON: When, I'm still not sure
13 that I've got it stated, that I've seen it stated
14 anymore, exactly what the sample size determination is
15 going to be, that we should review and comment on.

16 And also with respect to the picture on page
17 30, you've indicated the affects of choosing the spread
18 of amount ingredient handled under the two different
19 scenarios, one where they're spread out within each
20 cluster and one where they're spread out between
21 clusters.

22 And have, does the Task Force have an
23 indication of what they're planning to do with respect
24 to those? Both the sample size issue and the spreading
25 of active ingredient within each of the scenarios.

1 DR. HOLDEN: Yeah, what may not be clear,
2 I think we're, in this document we were trying to
3 propose a, like I say, I'd say a process.

4 And I think it's important to us that there
5 be some sort of goal and a goal that is of interest.
6 And from that point on whatever is reasonable, you
7 know, we're okay with.

8 I think that we needed to propose something
9 and we've, I've proposed something that, with checking
10 with the Task Force, that was something that seemed to
11 be reasonable to them and seemed to be something, I'm
12 not saying they can live with, but something that was
13 getting at the goal that they were interested in.

14 That's not saying there are better goals and
15 likewise the issue of the, you mentioned about the
16 cluster configuration being important, what we do in
17 that case, in reality I think I might have said that in
18 the document. But in reality we're never going to have
19 one of those configurations or the other.

20 The studies done in the past tended to be
21 more like this first configuration. Let me put that on
22 that I forgot what it was but there it is, whoops,
23 there it is.

24 Yeah, studies done in the past tended to be
25 like the first configuration with maybe these pounds

1 per AI handled more closely together, not spread out.

2 Studies that the AHETF has done, at least
3 some of them so far are more like this.

4 So, but there are many situations where for
5 many different reasons they had to, they fall, the fall
6 somewhere in between. And so I sort of gave two
7 extremes and looked at the power there.

8 So whatever is done, again, this is going to
9 depend on Doctor Portier's solution to all the errors
10 of the design. But given that it's something analogous
11 then configurations like this will probably have to be
12 investigated and we would then gear our sampling to try
13 to pick the optimal configuration within bounds, within
14 the restrictions of the logistics of course.

15 DR. HEERINGA: Yes, Mr. Lunchick.

16 MR. LUNCHICK: I just wanted to add also,
17 what we're really looking for from this panel is, are
18 the processes that have been proposed by the
19 statisticians to help us in determining the sample size
20 proper?

21 As we get into looking at different scenarios
22 we'll be sitting with the regulatory agencies and
23 knowing the magnitude, or having a good understanding
24 of the magnitude of exposure, what patterns are very
25 critical in agriculture, others which are kind of

1 unusual, things like that that will go into a consensus
2 on the accuracy that we would need and things like that
3 to determine the actual sample size and the clustering.

4 But we wanted to make sure as we do that that
5 whatever process we're using, people agree with and not
6 at the end of the process tell us, you shouldn't have
7 done that.

8 DR. HEERINGA: I think that the panel will
9 certainly be in a position to do that.

10 I think Doctor Johnson's question really gets
11 at how much error is tolerable? Because, I mean that's
12 where we as statisticians start and work backwards.
13 And I think you've gone through that, Doctor Holden,
14 with the Task Force.

15 And I think where you're at looks, I mean
16 it's very reasonable in some respects and we'll hear
17 more details from other people.

18 But when we factor this all into the
19 regulatory process where it ultimately goes, you are
20 going to want to have some level of accuracy or
21 precision in these data for generalized purposes. That
22 really makes the data not the determinant in whether
23 you get registered, I mean the data itself, but not the
24 error in the data, determinant to whether you get
25 registered or not on a product.

1 So we've got MOEs of 100, two orders of
2 magnitude. Would a third of an order of magnitude be
3 acceptable level of error for Doctor Johnson to work
4 with?

5 I mean that means that your errors in
6 estimation are a third of the, say one, you know, one
7 component in the total margin of exposure.

8 Are those, that sort of thinking, that's the
9 way I think about it naively but is that the way where
10 you're really sort of headed when you

11 DR. HOLDEN: Yeah, that's the idea that we
12 were headed with that.

13 I can't comment on the, like MOEs and things
14 like that but when I discussed with the Task Force
15 these are the way, these are exactly the, what you're
16 saying is exactly the approaches that they were
17 thinking.

18 And that's where I came up with the idea of
19 the fold accuracy with leaving the, that specific
20 number up to the people who really know better than me.

21 DR. HEERINGA: All right. I wonder if I
22 could ask Jeff Dawson or Jeff Evans too, maybe to
23 comment on this issue, or someone who is familiar with
24 that process.

25 I mean as you think about it what we're

1 trying to do here is to put this sample design in a
2 perspective where the data should not be, at least
3 errors in the data should not be the determinant of the
4 decision, that we can see through the errors to see
5 enough data to make decisions incorporating your other
6 uncertainty factors.

7 MR. DAWSON: Jeff Dawson. I think we'll
8 probably need to clarify this a little bit more because
9 this is a fairly, a question with many levels and it
10 really, to focus everybody on this issue I'd like to
11 remind everyone that FIFRA related to occupational risk
12 assessments and the risk management decisions that we
13 make, is really a risk/benefit statute.

14 So essentially the answer can vary in a
15 practical sense, depending upon, you know, the
16 situations that we're considering. And certainly we
17 consider these in the risk context relative to let's
18 say the severity of the toxic effect, the relative
19 steepness of the dose response issues that are
20 associated with the chemical.

21 And also as specified under the statute the,
22 you know, the associated benefits.

23 As far as, so those are the factors that we
24 consider when we make decisions relative to what MOE is
25 going to be the number that we can live with or we

1 can't live for risk management.

2 As far as the relative uncertainties or the
3 error that we're talking about now, I think we need to
4 think about it some and, you know, maybe talk a little
5 bit more about it in the morning.

6 DR. HEERINGA: Again I didn't want to
7 necessarily suggest that there is one number.

8 MR. DAWSON: Right.

9 DR. HEERINGA: But I think some notion of
10 scale as to how, because when, if you go one to
11 probabilistic work later on or if you work
12 deterministically with the model that we've seen today
13 you will want to put some uncertainty bounds on that.

14 And if those uncertainty bounds are
15 excessively large due to variability and uncertainty in
16 the actual input data, and we've seen that a lot over
17 the years, I think here's a chance to sort of say, you
18 know, we want to be practical, we want to be cost
19 effective, but we also want to make sure that what we
20 deliver has essentially a small enough uncertainty in
21 it that it's not going to ultimately be the determinant
22 as to whether we can or cannot make a risk decision or
23 a registration decision on a project, a product.

24 MR. DAWSON: Uh-huh. David Miller wants
25 to answer.

1 MR. MILLER: I just, in terms of, we, when
2 we first looked at this we didn't think the goals
3 established on that were unreasonable.

4 But we did note that there are, and it's, I
5 mean the percentile, for example the K-fold. I mean we
6 can, we may alter those later, it's essentially kind
7 of, as much a risk management decision as anything
8 else.

9 So I think what we're asking more of the
10 panel is to the extent that, in terms of the
11 methodology being used by the Task Force in order to
12 determine the number of clusters, et cetera.

13 We can decide at some later point we want a
14 higher percentile or we want a different K-fold and
15 that should be relatively easy I think just to go back
16 and kind of recalculate some of that information.

17 And that's the first aspect and the second
18 aspect, just keep in mind kind of where we're at now,
19 which in essence looking at a central tendency, 50th
20 percentile geometric mean type thing.

21 So just kind of, it looks a lot better than
22 where we're at now and just in terms of specifics, in
23 terms of the K and the percentile that you're trying to
24 cover with a certain degree of confidence, that seems
25 to be, I mean something we can decide at the Agency in

1 terms of any discussion with risk managers.

2 DR. HEERINGA: One other thing just to set
3 us up for tomorrow too. Doctor MacDonald pointed out
4 that it will make a difference at which quantile of
5 this distribution, the median or the central tendency
6 of 1, but if you were to jump out to the 95th
7 percentile

8 MR. MILLER: Uh-huh.

9 DR. HEERINGA: it could affect our
10 response on this.

11 How, I don't want to put you on the spot but
12 in the larger context of thinking about this database
13 and its utility for five or ten years

14 MR. MILLER: Uh-huh.

15 DR. HEERINGA: is that something that
16 should be consider on an equal basis with the
17 historical use of the

18 MR. MILLER: For example up to the 95th

19 DR. HEERINGA: Yeah.

20 MR. MILLER: for example the 95th
21 percentile?

22 DR. HEERINGA: Yes.

23 MR. MILLER: I'm thinking, just thinking
24 into the future that would not be an unreasonable thing
25 for us to consider.

1 DR. HEERINGA: And that's just in terms of
2 planning for this data set and what it ultimately might
3 be used to look at.

4 MR. MILLER: Yes.

5 DR. HEERINGA: Okay. Doctor Popendorf.

6 DR. POPENDORF: I guess I'm not quite sure
7 what your question was to the degree that, I mean, like
8 Table 4 in the report or somewhere here they have
9 looked at the 95, 95th percentile.

10 Are you just saying, should we look at that
11 or

12 DR. HEERINGA: I was trying to get at some
13 sense of whether that's there for demonstration or
14 really should we be looking at the results that have
15 been, we'd be primarily focusing on results that look
16 at, at means and say, medians as opposed to something
17 that is out a little further in the distribution?

18 And I think the answer is, we should look at
19 all of them equally in terms of our comments tomorrow.

20 Cynthia Hines.

21 DR. HINES: Just a clarification. I
22 understand that our primary objective at this point is
23 to look at the process. And this might be more
24 directed at the Agency.

25 In their document, Table 5.2 on 102, page

1 102, there are proposed AHETF sample sizes, so I mean
2 is that kind of just a, is that really in the works or
3 are we really further up the stream than I'm
4 confused.

5 MR. MILLER: You're talking about the
6 Agency's document on that.

7 I think there's a sentence in there that says
8 that these are essentially kind of a first cut at
9 looking at things. And depending on what the panel
10 kind of discusses and the conclusions and the thoughts,
11 that obviously could be changed depending on where the
12 Agency wants to go.

13 But that's a kind of a first cut at looking
14 at things.

15 DR. HEERINGA: Yes.

16 DR. COLLIER: I'd like to respond to it

17 DR. HEERINGA: Doctor Collier.

18 DR. COLLIER: from the perspective of
19 the Task Force, Richard Collier with the AHETF.

20 That information was provided by the Task
21 Force to EPA. It was preliminary information,
22 information we used initially in our scoping process
23 and in setting an overall budget.

24 However the process for determining the
25 sample size for individual scenarios that's been

1 described to you this afternoon is the process that we
2 expect to use going forward.

3 So that table had many early uses but
4 shouldn't be considered what we consider a roadmap at
5 this point.

6 DR. HEERINGA: I think that we're going to
7 plan to reconvene tomorrow morning for a continuation
8 and a discussion of this charge.

9 Before we break for the afternoon though, is
10 there any member of the panel that really has sort of a
11 different twist on this, something that you'd like to
12 sort of lay out there quickly before the evening so
13 that people would have a chance to think about it and
14 potentially prepare to react to it?

15 I guess what I, you know, if anybody is
16 expecting to throw a curve ball, throw it now.

17
18 DR. LEIGHTON: I've got one.

19 DR. HEERINGA: Okay, introduce yourself.

20 DR. LEIGHTON: I'm Tim Leighton from
21 the Antimicrobial Division.

22 The document that we provided you also has a
23 sampling plan for the Antimicrobial Task Force. That
24 showed I think 19 studies, 15 replicates each. That 15
25 replicates was based on our guidelines for the minimum

1 recommendation.

2 So any comments along those lines would be
3 helpful for us also.

4 DR. HEERINGA: Thank you very much, Doctor
5 Leighton. Doctor Popen Dorf.

6 DR. POPENDORF: Yeah I'm, not exactly a
7 curve I guess but I was going to ask the question
8 yesterday, I think that was yesterday, to the person
9 from the Aerial Applicators Association.

10 And it kind of goes back to question 4 I
11 think and also maybe applies to this, that maybe you
12 could, I don't if tonight, today or tomorrow, but the
13 statement was made that in that study there was no
14 correlation with active ingredient.

15 And I was wondering two things: One, were
16 there any correlations with anything else and, you
17 know, how, that would seem like it might be a good
18 example to talk about, both in terms of the
19 implications of study design here in this clustering,
20 it's like a case study?

21 And also going back to question 4 for an
22 example of something that doesn't correlate with active
23 ingredient handled.

24 DR. HEERINGA: I'm not sure that the AHETF
25 is directly involved there, that was

1 MR. LUNCHICK: Yes we are.

2 DR. HEERINGA: Andrew Moore I think from
3 the

4 MR. LUNCHICK: Yeah but I could, this is
5 Curt Lunchick from the AHETF.

6 That is a study we cooperated with the USDA
7 APHIS on, and we have not completed the analysis of the
8 data and at this point haven't made recommendations,
9 interpreted everything it means, so I can't really
10 answer your question except for those are things that
11 we will be looking at too.

12 I mean there's other issues with the aerial
13 data, the ULV applications versus normal spray volumes
14 that we need to address and that will be done in
15 conjunction again with EPA, DPR and PMRA to make sense
16 of it and make recommendations on whether we have
17 sufficient data or if we need to obtain more.

18 DR. HEERINGA: Thank you very much Mr.
19 Lunchick.

20 Any other comments or inputs now, things that
21 you'd like to put out there that the, all of us may
22 want to think about some more this evening in
23 preparation for tomorrow?

24 DR. JOHNSON: Steve, this is kind of minor
25 but I wonder if it would be possible to get electronic

1 versions of the PowerPoint slides that have been
2 presented?

3 DR. HEERINGA: Is that possible to provide
4 those? I think they would be part of the docket,
5 right?

6 MS. CHRISTIAN: Yes.

7 DR. HEERINGA: I, Mr. Lunchick or Doctor
8 Collier, is it possible to get copies of the electronic
9 presentations from the AHETF?

10 DR. COLLIER: They have been provided for
11 use in the docket. I guess I'm not sure we have the
12 capability to make copies of those overnight though.
13 Perhaps a copy or two might be able to be generated.
14 If you

15 DR. JOHNSON: I'm not saying

16 DR. COLLIER: specifically

17 DR. JOHNSON: yeah, I'm not thinking
18 about overnight, I'm thinking about it as we write up
19 our report and review it and so on.

20 DR. COLLIER: Oh, certainly.

21 DR. JOHNSON: It gets terribly, I have a
22 terrible time searching through the documents to find
23 things and it would be much nicer to be able to search
24 through the PowerPoints there.

25 DR. COLLIER: We will certainly cooperate

1 with the Agency and

2 DR. JOHNSON: And so you could just email
3 them or whatever, it would be fine.

4 DR. HEERINGA: Actually if they have been
5 provided for the docket we'll take care of it from the
6 SAP, so you should not worry. I just want to make sure
7 of permission on that.

8 DR. COLLIER: Yes.

9 DR. HEERINGA: Okay then, unless someone
10 else has something else for this afternoon, I'd like to
11 thank everybody for their participation today. It's
12 been a very productive session. I think we've had some
13 very interesting discussions.

14 And again our plan for tomorrow will be to
15 convene at 8:30. At that time we will pick up on a
16 review of some points from the previous few days and
17 then return to the charge question on sample size.

18 So we'll see everybody tomorrow morning at
19 10:30. Have a good evening.

20
21 (WHEREUPON, the meeting was adjourned for the day.)
22
23
24
25

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

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4 I do hereby certify that the witness in the
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17 I certify that I am not a relative or employee of
18 either counsel, and that I am in no way interested
19 financially, directly or indirectly, in this action.

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22
23
24 MARK REIF, COURT REPORTER / NOTARY

25 SUBMITTED ON JANUARY 11, 2007

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