FIFRA SCIENTIFIC ADVISORY PANEL
OPEN MEETING

REVIEW OF WORKER EXPOSURE
ASSESSMENT METHODS

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FIFRA SCIENTIFIC ADVISORY PANEL (SAP)
Review of Worker Exposure Assessment Methods
January 10, 2007
Morning Session

DR. HEERINGA: I'd like to welcome everyone back to the second of four days in our scheduled FIFRA Scientific Advisory Panel Meeting on the topic of a Review of Worker Exposure Assessment Methods.

I am Steve Heeringa of the University of Michigan. I'm an applied statistician. I currently Chair the FIFRA SAP and will serve as the General Chair for the meetings today, tomorrow and Friday morning as needed.

I want to make one administrative note. I do have a teaching obligation this afternoon at the University of Maryland and I'll be away and Doctor Portier will be assuming duties for chairing the session just for this afternoon. I'll be back tomorrow morning.

What I'd like to do before we turn to the morning proceedings is to again thank members of the panel for committing time at a very early part in their academic or research year here to come to D.C. for this very, very important session. And I'd like these

individuals to introduce themselves and provide some background on the affiliation and relevant expertise. Ken.

DR. PORTIER: I'm Ken Portier, Director of Statistics at the American Cancer Society National Home Office in Atlanta. And my interest is in probabilistic issues in risk assessment.

DR. HANDWERGER: Good morning, I'm Stuart Handwerger from the Departments of Pediatrics and Cell and Cancer Biology in the College of Medicine at the University of Cincinnati. My clinical expertise is in pediatric endocrinology and my research is in developmental endocrinology.

DR. CHAMBERS: I'm Jan Chambers with the College of Veterinary Medicine at Mississippi State University. My area of expertise is pesticide toxicology. I'm a member of the permanent SAP and I'm also a member of the EPA's Human Studies Review Board.

DR. BUCHER: I'm John Bucher, I'm with the National Toxicology Program at the National Institute of Environmental Health Sciences. I have an interest in carcinogenesis bioassays and the development of new toxicology methods.

DR. HINES: My name is Cynthia Hines. I'm a research industrial hygienist with the National

Institute for Occupational Safety and Health. My research areas are in occupational exposure assessment studies, including a number of pesticide field studies.

DR. JOHNSON: My name is Dallas Johnson. I'm retired recently from Kansas State University where I served in the Department of Statistics and as a consultant for the Agricultural Experiment Station for more than 30 years.

DR. APPLETON: I'm Hank Appleton with the U.S. Forest Service. I'm a pesticide toxicologist and I prepare exposure assessments and risk assessments for the pesticides that we use in our pest management programs.

DR. KIM: I'm David Kim from the Department of Environmental Health at the Harvard School of Public Health. And my work is in the human exposure assessment and pharmacokinetics.

DR. BARR: I'm Dana Barr, I'm from the Centers for Disease Control and Prevention in Atlanta. I'm the Chief of the Pesticide Laboratory. And my research interest is in human exposure assessment, primarily through bio-monitoring.

DR. LU: Good morning, Alex Lu from the Rollins School of Public Health at Emory University. My interest is in using biomarkers to assess pesticide

exposure and use the pharmacokinetic model to interpret those biomarker results.

DR. HUGHES: My name is Brian Hughes, I'm a toxicologist. I work with the Michigan Department of Agriculture in the pesticide section with my interests being in the risk assessment, cooperating a lot with Michigan State University doing field studies for occupational risk assessment for ag. workers.

DR. LANDERS: My name is Andrew Landers. I head the Application Technology Group at Cornell University. Our interest in the team is to look at engineering ways of reducing operator contamination in environmental pollution.

MS. MCCARTHY: My name is Peter MacDonald, I am Professor of Mathematics and Statistics at McMaster University in Canada. General expertise in applied statistics and this is my seventh year on FIFRA panels.

DR. HAMEY: Good morning. I'm Paul Hamey, I'm from the U.K. where I work with the U.K. government's Pesticide Safety Directorate which is our regulatory agency for agricultural pesticides.

DR. ROBSON: Good morning, I'm Mark Robson, I'm the Director of the New Jersey Agricultural Experiment Station and Professor of Entomology at

Rutgers and Professor of Environmental Health at UMD. My research interest is to look at pesticide exposure to farmers, and most recently to pesticide exposure to children.

DR. POPENDORF: And I'm Will Popendorf, Professor of Industrial Hygiene at Utah State University. My specialty area is exposure modeling and control and I have probably 30 years experience in pesticide exposure assessment.

DR. CURWIN: Hi, I'm Brian Curwin with the National Institute for Occupational Safety and Health. I'm a research industrial hygienist, conducting occupational exposure assessment studies for pesticides generally.

DR. HEERINGA: Thank you again, panel members. At this point in time I'd like to introduce the Designated Federal Official for today's meeting and the balance of the meeting, Myrta Christian.

MS. CHRISTIAN: Thank you, Doctor Heeringa, good morning. I would like to welcome everyone to today's meeting to consider the review of worker exposure assessment methods.

Again I would like to thank the panel, the presenters and the public for participating in this meeting.

Also, I would like to remind everyone that all the documents related to this SAP meeting are available in the EPA docket and in the SAP website.

I look forward to another day filled with lively discussion and great panel participation.

DR. HEERINGA: Thank you. Just to recap where we are, yesterday's session was primarily an information and presentation session. We heard in the morning an introduction and overview on worker assessment methods within the EPA in general and elsewhere from Jeff Evans and an historical perspective on the worker exposure assessment from John Worgan of Health Canada, the Pest Management Regulatory Agency. We also heard case studies, just sort of a general introduction as to how EPA uses the data form the PHED system currently and a discussion from Cassi Walls of the Antimicrobial Division on how the Antimicrobial Division would potentially incorporate findings and recommendations that came forward from these panel meetings. Then in the afternoon we had a presentation from the AG. Handlers and the Antimicrobial Exposure Task Forces form industry and we had a period of public comment.

And I wanted to make a note for the record that we did receive yesterday a written comment from

Doctor Richard Fenski of the University of Washington. That comment, the panel has copies of that two page written submission and it will be placed on the docket for this session as well. So just in the interest of full disclosure that is also available to the panel.

Okay, what we would typically do in these multi day sessions is to include in the first session each morning sort of recapping events of the previous day and provide the EPA scientific staff a chance to sort of update or maybe amend or extend some of the information that was provided yesterday.

So at this point in time I'd like to turn it over to Jeff Dawson and Jeff Evans of the Health Effects Division of the Office of Pesticide Programs.

MR. EVANS: Thanks, Doctor Heeringa. We've got two items for followup from yesterday, one a clarification from a representative of the Agricultural Handlers Exposure Task Force regarding one of the slides addressing data generation and Jeff Dawson some corrections to announce.

MR. DAWSON: Believe or not we made an error. Just for clarification since we're on the agenda today, we're talking about the biological monitoring issues. In the background document one of the ratios which we've calculated is in error so I

don't, I'm not sure that we're presenting it today but we can have copies made of the corrected page and distribute them to the panel.

And specifically it's on the Table 3.2 for Malonate and the ratios there are incorrect because we made a math error.

DR. HEERINGA: Thank you very much for citing the Table too, that's now part of the record as well.

Any additional introductory comments? I understand, Mr. Dawson, that we also will have Doctor Collier is going to, from the AG. Handlers Task Force is going to have a few additional comments to follow up on yesterday.

DR. COLLIER: Thank you. I'm Richard Collier, the current Chairman of the Administrative Committee of the AG. Handlers Task Force.

It's come to my attention that there might be some lack of clarity about one of the slides that I presented yesterday, specifically slide 16 which was entitled PHED's data dilemma. One of the bullet points on that slide indicated that some 100 studies have been submitted since 1995 that are not included in the PHED database and the final slide there indicates no incentive to industry to submit new studies. That may

seem to be an inconsistency. The intent of the last bullet was to indicate that there was no incentive for industry to submit new studies for inclusion in the PHED database. Many studies were submitted, more than 100 since 1995 in response to product specific data requirements of the Agency, but those studies were not submitted by the industry for inclusion in the PHED database because of the data compensation issue. I just want to clarify that point.

DR. HEERINGA: Thank you very much, Doctor Collier. Any questions from the panel on either of these two items?

Okay, well let's get underway with today's program. The first presentation we have is going to be given by Doctor Sheryl Beauvais of the California EPA Department of Pesticide Regulation. Doctor Beauvais.

DR. BEAUVAIS: Good morning, I'm going to be talking about I'm getting feedback, are you also? Okay, don't worry about it, okay.

This morning I'll be talking about comparisons between biological monitoring and passive dosimetry. Basically we've got a database out there that consists of studies done by one or both methods and what we've done, EPA's done a lot of this work, other researchers have done work and I'm going to be

presenting some of that with the intent of showing that, if we compare results from these diverse methods, and they generally are converging on similar values, then that suggest to us that we might, that these methods are somewhat supportive of one another. May I have the first slide please. Thank you.

On the background, this, materials in the background, Section 3 of the background document, I'm going to be covering the majority of Section 3 and then the last part of that with the hand exposure methods. Jeff Dawson and Jeff Evans will be presenting afterwards. And in that Section 3 of the background document we discuss three key issues, there's a section in there that talks about that, and four key issues are listed, I've got three of them on the slide here.

The first one the main concern that we have here is we want to be sure that there is not a potential for a systemic bias, that there's not evidence to suggest that and possibly evidence to suggest that there is not a systemic, systematic bias, sorry, between biomonitoring and passive dosimetry methods. And then the other three key issues that were identified are really subsets of that. We're concerned very much that passive dosimetry not underestimate exposure because the bulk of those studies in, no, all

studies in generic databases and the bulk of the studies that we use in exposure assessment rely on passive dosimetry, and if it's underestimating exposure that's a concern.

And so the other issues deal with ways in which, or proposed ways, mechanisms by which passive dosimetry might underestimate exposure. And the second bullet there is the first of these which is dermal absorption. There is concern that residue may be absorbed dermally during attempts to remove it. And I'll talk more about that in a little bit. But essentially that would result in a positive, possible negative bias if in, while attempting to remove the residue we are actually encouraging it to absorb through the skin or fail to collect it, then that can result in an underestimate.

And then the other one generally is residue breakthrough form whole body dosimeters. And I'll talk more about that shortly. And again that can result in a positive, possible negative bias. And the other one has to do with hand exposure methods and I'll defer that to the next presentation. Next slide please.

Okay, one way to think about passive dosimetry in biomonitoring here, I'm going to start at the lower left of the slide, is essentially pesticides

are contacting the skin, contacting the body surface during a person's workday and they are absorbed, metabolized, distributed through the body and excreted ultimately.

And moving you up to the upper right, the active compound, the active, whether it's the pesticide or it's metabolite, whatever it is that's toxicologically active, the moiety, when it reaches its target, whether it's an enzyme or other type of tissue is basically if we had a way to look at that, if we had for example a Star Trek Tricorder where you could wave it in front of the person and say, yes, there's this much damage happening right, if we could actually see that in the compound episode of injury and know quantitatively what was happening we would have.

And if we could do the same thing in toxicology studies in animal data where you could say, yes, this is, you know, if this dose is happening at that site, this is the damage that's occurring and we could compare those two numbers, we would have perfect risk estimates.

But we don't have that, so instead we have a couple of surrogate approaches that we can use. And with passive dosimetry, essentially we're trapping the pesticide before it reaches the body, either on

clothing, on patches or we are removing pesticide before it's been absorbed if we're doing a dermal absorption removal. In the case of inhalation we're trapping pesticide in the breathing zone area.

So that's one approach is we're quantifying the amount of pesticide reaching the individual.

The second approach is down in the lower right, is biomonitoring where we're actually quantifying residues that are excreted or are in the system in blood or other tissues. So we're actually taking the amount that's absorbed and that has been metabolized or processed or is, and is actually in the system itself.

Generally we're taking urine sample, excreted amounts and we're quantifying that so this is so we have sort of the before and after. These are both surrogate approaches to get us, for what it is we really would like to have in a perfect world where we know exactly what the toxicologically active amount is at the target site. Next slide please.

So we've talked about, a couple of presentations yesterday talked about passive dosimetry, so I'm going to quickly go through these again in just another perspective. It measures the amount of the pesticide that's impinging on the surface of the skin

or the amount available for inhalation. So we're either absorbing or removing dermal residues or we're trapping residues in the breathing zone in the case of inhalation.

We'll talk an awful lot about dermal exposure because dermal is, in most scenarios the dominant exposure route unless you're dealing with a volatile compound like a fumigant for example. Next slide please.

And we, you've seen some, already some slides on monitoring dermal exposure.. This fellow who is all dressed up here has, these are patches and they show those. That's one common methodology. And I wanted to show, this is slide that you wouldn't have seen before, we talked, we're going to talk in a minute here about the backing that, about an impervious barrier and that's kind of small but that's, what you have is absorbent material and then an impervious backing behind it. And this patch when it's torn away a little bit you can see that. So that we have, the patches that are placed at various locations on the body and in the case of each patch you're assuming that, and extrapolating the residues found on the patch to a certain region of the body. The arm for example, the leg, the chest, whatever.

In contrast, the whole body dosimetry, we have, and this is a whole body, the photo is of a study that was done to measure residential exposure but this is a full body dosimeter and give you the sense of what that is, and you've seen photos of this yesterday as well, but it's a garment that covers the body basically from the shoulders to the ankles. It does not have an impervious backing obviously. And so one of the concerns that we have is about the potential for pesticides to pass through that barrier and fail to be measured for that reason. Next slide please.

When we're talking about, when we monitor exposure to the head and the hands now, when, the slide that I just showed you we had, all we were talking about were trapping methods when you're talking about the majority of the body. We don't do residue removals in anywhere except pretty much the head and the hands in general. And so in each case we have a trapping method and a residue removal method so that a trapping method might be gloves or a patch, you can put patches on the head, attached to a hat perhaps and some studies have used headbands or hats, you could have a collar patch for example. So there are many approaches that way.

The most common way that's currently being

used are face and neck wipes and this is a residue removal method where you are soaking some sort of an absorbent pad with a solvent or a surfactant solution and wiping as much of the exposed, ideally wiping the entire exposed area. And this is, we have concerns about residue removals methods because there's a question about whether you were actually getting all the residue that's on the skin. And again that's a concern because of the potential to underestimate exposure if you don't get that because you're analyzing what you've removed.

Again with hands you've got gloves that would trap residues or rinses or hand, hand rinses, hand washes, hand wipes where the residue that's on the, their hands is wiped away or rinsed away and you're measuring the amount that's been removed from the hands.

So when we take those, in yesterday's slides you saw a couple of times in yesterday's presentations the equations that are used to estimate total exposure, dermal exposure from these methods. We essentially take, when you're talking about dermal exposure we take the residue from the dosimeters, whatever has been removed and combined with other factors such as dermal absorption which comes from animal or human data, an

estimate of the body's surface area if you had patches, and then any sort of protection factors. If you were measuring outside clothing but the person was, would be wearing clothing then you might incorporate protection factors into your estimates. Each of those is, incorporates its own assumptions or defaults and those again are potentials for error in the passive dosimetry based estimates.

And with inhalation exposure we trap residues in the breathing zone, this is the predominant way that this, that inhalation exposure is estimated. You see this fellow here with the sampling pump on his, attached to his belt and then a tube that runs up over his shoulder and then the end of that sampling tube is pointed downwards from his shoulder. And this is, it's intentionally facing downwards so that it's not contaminated with deposition pesticide settling out from the air.

The sampling pump is running at a fairly low rate, something like 2 liters per minute which is less than the breathing rate, so you're going to have, so we do a calculation for that as we make an estimate of the breathing rate that the person might have had from, depending on their level of activity, their age and so forth. But, oh, in, and then, also, I'm sorry, at the

top of the tube here is where the sampler, the material that's going to collect the residue is located, it's a resin charcoal or something like that up in the sampler tube. And that's what's analyzed, the sampling tube is, the material within that is extracted and analyzed.

And again in, using this in, to estimate inhalation exposure we would deal with inhalation rate. Absorption factors, we have very little data on that, we generally assume 100% absorption. If it's available in the breathing zone we assume that they've inhaled it. And then protection factors for a respirator if the, if they're required to wear one in that scenario.

So we have several assumptions with passive dosimetry. We assume that the residues that we measure are meaningful indicators of exposure, we assume that those, the residues that we've measured that are on the skin surface or trapped in dosimeters and so forth are available for absorption, that's one assumption. We also assume either that the, we assume if the duration of the monitoring differs from the duration of actual, the scenario that we're trying, the working interval, whatever, that that doesn't matter. Now we do have data that suggests that shorter intervals will tend to, you'll tend to get higher exposure estimates than if you measure over longer intervals. So that in general

we try to have the monitoring intervals match the intervals of the scenario that we're trying to estimate exposure for. So in most cases it's a full workday for occupational exposure.

We also assume that the dose that is absorbed through skin, the dermal absorption, whatever value we're using, we're assuming that that can be extrapolated from the laboratory data, whether it was in, from human volunteer studies or from animal data, that that's a meaningful number. And then finally if we uses patches and we've done an extrapolation we're assuming that the residue on the patch really could be generalized to the entire region. Or that that extrapolation is valid.

Passive dosimetry gives, has several advantages which is why it's so widely used. It allows the differentiation of exposure for one thing. You can tell what part of the body if, how much of this was dermal, how much of it was inhalation. It allows you to differentiate between activities in a workday if a person can switch, can change clothing for example. You can monitor a portion of their workday only. And also because it allows you to differentiate between body parts, it allows you to evaluate measurements that would be, tend to reduce exposure. For example, if

there is a great deal of exposure on the hands then we could evaluate the use of gloves, how much that affects it. Because the monitoring is occurring during the working interval you can supervise the subjects during the entire period that you're collecting the data. And because of the assumptions that were discussed yesterday that for handlers, that exposure is independent of the, largely independent of the chemical characteristics of whatever the active ingredient is, you can use studies, surrogate data from one study to, form one chemical to estimate exposure to another.

Disadvantages of passive dosimetry is that it requires an estimate of dermal penetration and that's a big one, that's, we need to use surrogate data from laboratory animals a lot of times, many active ingredients don't have data from human volunteers and also there are studies that suggest that dermal absorption varies with the amount of the pesticide that's on the skin, which makes sense. If you load a great deal of pesticide on, or a great deal of material on the skin, proportionately less of it gets absorbed. The absolute absorption may be higher but proportionately less of it is absorbed. And we also have uncertainty because we have various methods of estimating dermal exposure so that you, if you're

comparing between studies you may have one study, and this was discussed yesterday where the patches were placed in one location and another study where they were placed in another, so that that, there's variability between studies.

Biological monitoring is essentially an estimate of the internal dose, how much was absorbed. And it, to do that we, to the, to collect those data we're measuring the body burden of a chemical, either the pesticide itself or the metabolites of the pesticide in selected tissues such as blood or the amount that's excreted from the body of the, either the pesticide or its metabolites. For practical reasons, because it's just very, it's much easier to get people to collect urine than it is to draw blood and it's just much easier to go with urine samples. And so that's the majority of what we're talking about when we talk about biomonitoring, this is usually urinary. Next slide please.

Biomonitoring also has several assumptions. We, it assumes that the urine is the major route of, is a major elimination route for the pesticide or its metabolites. To the extent that it isn't you're dealing with extrapolation errors. It's also assuming that the residues that are in the urine were entirely

due to the pesticide that was absorbed during the activity that you were monitoring. So during that work shift. If there are other ways for the metabolite or for that pesticide if there was exposure outside of that, if you have a metabolite that's common to other compounds besides the pesticide of interest, then you'll have, that undermines that assumption. And also we assume that pharmacokinetics can be extrapolated from laboratory studies and that it's relatively consistent between individuals, that the data that we get again from the laboratory are meaningful out in the real world.

And biomonitoring offers the advantage that it's integrating exposure across all routes. It doesn't matter whether the dose was absorbed dermally or by inhalation or by ingestion. Assuming that we have sufficient pharmacokinetic information we can get a good absorbed dose estimate. And we also do not need an estimate of dermal absorption with biomonitoring which is a good advantage of that.

It has disadvantages as well and the biggest one for that is that we require the pharmacokinetic studies in order for this, these data to be useful. And also there is some inherent variability in pharmacokinetics. We metabolize, pesticide might be

metabolized and absorbed at different rates between people and at different times within the same person. It also requires a greater degree of, biomonitoring requires a greater degree of cooperation from the study participants because they need to save their urine and they need to be honest about the extent to which they've saved it because we generally are operating off of 24 hour samples. And also the results can be absorbed by, can be affected by other absorbed materials. Again if they've been exposed to the pesticide at other times or if they've been exposed to something that gives the same metabolite as the one that we're monitoring.

And also we mentioned the characteristics. If we had the ideal target compound for biomonitoring, these are the characteristics it would have, it should be either the pesticide itself if it is excreted unchanged or a major metabolite of the pesticide. And again that's to minimize the errors of extrapolation. If you're dealing with something that's 10% or less of the absorbed dose, then you're extrapolating, you know, an order of magnitude or more. We also want it to be ideally specific to the pesticide of interest. If it's a metabolite common to a lot of compounds it's much less useful. And we want it to have a valid analytical

method obviously and it should be stable so that it's actually present throughout the sampling interval and up until the point of analysis. So the example that I've shown up there is the one that's the classic, the 346 Trichlorpyr and all the TCP that's the metabolite of Chlorpyrofos.

So I'm going to talk about some comparisons now between biomonitoring and passive dosimetry. And the rationale again for our comparisons is that we have these two very diverse methods that are used too estimate exposure. There, we have good data, a substantial database for both that would give us good data for comparisons and each method, although each method has its advantages and disadvantages, you know, the, they, together we can, if they converge again on the same values then we have greater confidence in the values that there, both methods are reporting for us.

So first there are two different approaches that were taken in these comparisons. The first is concurrent studies, those are studies with simultaneous monitoring of passive dosimetry while collecting biomonitoring samples as well. So that the subjects wear the dosimeters and so forth and provide the samples. We're comparing the amounts calculated from passive dosimetry and biomonitoring and that's usually

the absorbed dose or it can be residues collected in urine and residues analyzed on the dosimeters and passive dosimetry. Next slide please.

There are uncertainties associated with passive dosimetry that will potentially affect these comparisons. One is if you have inconsistent techniques within a study. For example, variable patch placement, one person is wearing different types of PPE, et cetera that can affect those comparisons. Also, the use of fixed dermal absorption. As I mentioned before the amount of pesticide that's absorbed will vary with, can vary with the amount that's on the skin and we generally select a fixed value. For example, 3%, we say 3% of the Chlorpyrofos residue on the skin we assume to be absorbed and so we're using that as a fixed value and that can, that adds to the uncertainty of our estimate. Next slide please.

There are also uncertainties in the biological monitoring component of these comparisons. The accuracy and the variability of the pharmacokinetics, again that's an area that can add to our uncertainty, depending on the, how variable it is and how accurately we have estimated. If there are incomplete urine collections from the test subjects.

Also if there were previous unreported exposure to the same pesticide. To minimize the chance of that affecting the estimates most biological monitoring studies incorporate a pre-exposure urinary sample where they ask the test subjects to collect their urine 24 hours before they're exposed and then that gives you the idea of the background levels. And finally there is concern about if you, if whatever residues the passive dosimetry has intercepted are residues that weren't absorbed obviously, if they were collected on the skin they weren't absorbed through.

So the majority of these studies involved, with the concurrent monitoring involved chlorpyrofos and again that's because it has a really nice metabolite which is the TCP metabolite. There are many comparisons available of absorbed dose. The TCP is estimated to, roughly 70% of the absorbed chlorpyrofos is estimated to be excreted as TCP in these biological monitoring comparisons. We also have some samples of other organophosphate pesticides and some non-OP pesticides as well. In most of those cases we're correlating the residues rather than getting absorbed dose estimates.

So the first set of comparisons, these are ones that were reported by Fenske and Day. They were

reported by them from calculations that were made by Layton at EPA in the exposure assessment for chlorpyrofos and what you're looking at here is, across the bottom are just basically scenario numbers, these are just distinct handler scenarios. And there's a key up in the upper right here that would, that tells you which, the first two are mixer/loaders, applicators and so forth. And then on the, this, we're getting absorbed dose estimates or we're getting, I'm sorry, unit dose, unit exposure estimates, micrograms per kilogram of active ingredient handled. So these are actually the, what we call unit exposure rather than absorbed dose estimates. Each of the points on this graph is an arithmetic mean, arrow bars are standard deviation. And the main point that this makes for us is that in each of these comparisons the doses don't stray very far. The yellow is the biomonitoring estimate and the red is the passive dosimetry. And those are fairly similar. Next slide.

You see the same thing with, these are reentry studies, the last slide was handler exposures. And in this case our estimate is the total absorbed dose in this case, micrograms per kilogram body weight per day. And again, red is the passive dosimetry, yellow is the biomonitoring and each point in this, on

this one, these data are, were summarized by Honicutt, et al and I've simply graphed their estimates here. Each point is the geometric mean with the arrow bars being the standard deviation and these are four different scenarios of, and during which they had concurrent biomonitoring of passive dosimetry.

There are also several other studies available that are reported in the literature. And some of those did have compound specific metabolites, a metabolite that was specific to the active ingredient being monitored. In a lot of cases for organophosphates what's monitored instead are metabolites that are common to many OPs, dialkyl phosphate metabolites for example, where you can monitor for multiple organophosphates at the same time. And there are numerous studies where those sorts of monitoring were done.

On this slide I mention a couple of examples of comparisons that have been reported. These generally are reporting correlations because you're not getting absorbed dose estimates off those. You can't assign the metabolites to a specific pesticide so we don't have absorbed dose estimates for specific pesticides so that they're not always calculated. But the correlations did involve a range of exposures and

the correlations are, can be fairly, fairly good. Next slide please.

So these had good to moderate correlations in some of these studies. For example, when they were estimating absorbed doses and excreted alkyl phosphates for the applicators that were spraying Dimethoate in olive trees they recorded a correlation of r squared of .65 between the absorbed dose estimate in which they calculated by assuming a 10% dermal absorption, 100% inhalation. And then they correlated that with the alkyl phosphates excreted in the urine.

In some studies there were poorer correlations, although in many or those studies they had small sample sizes or they had documented previous exposures to the pesticide outside the interval that they were monitoring with the passive dosimetry. In complete passive dosimetry perhaps they were only monitoring the hands for example, or they had short intervals for biomonitoring. Biomonitoring need to be carried out for at least a few half lives of the compound to, you want to get a quantitative recovery of the compound.

There are also some correlations reported with pesticides that are not organophosphates. Dyfiopyr is an example of a compound that's had

concurrent dosimetry and biomonitoring done and they found, they had poor recovery in the biomonitoring samples unfortunately. There's also studies that have reported biomonitoring and passive dosimetry for Captan. Unfortunately Captan has a metabolite that's a very small portion of the absorbed dose so those studies generally haven't resulted in good correlations.

EPA put together some tables and those are the tables that Jeff Dawson mentioned before we began. There were two tables in this background document. The first is the 3-1 which is a report of ratios of passive dosimetry to biomonitoring estimates that were reported in EPA exposure estimates. These are essentially preliminary ratios. There wasn't any processing of these numbers, they're just reported as they were reported in the risk assessments. And they're, so they're ratios of passive dosimetry to biomonitoring and they've dealt with either absorbed doses or unit exposures.

The absorbed dose would be micrograms per kilogram body weight and unit exposure would be for the handlers, milligrams per pound AI handled. These, some of these were ratios of arithmetic means rather than geometric means. If we were to really put some work

into this we would actually want to do comparisons of all geometric means. But for, as ballpark estimates these ratios can give us sort of a sense of how well passive dosimetry and biomonitoriing correlated and we had a range of ratios which actually, as I'm reporting on the slide, the lowest one was .01 and the highest is 5.73. Now as I understand it the .01 number is going to be somewhat in dispute, that's coming from Propinyl. And I think the AG. Handler Exposure Task Force has something to say about that in a little bit.

But at any rate the important takeaway that we took from this is that neither method consistently overestimated or underestimated in that you didn't have consistently higher estimates for passive dosimetry or biomonitoring. And that they were all fairly close to 1 and they're all within an order of magnitude of 1, with the exception of the two numbers from Propinyl.

Another approach for comparisons of passive dosimetry and biomonitoring are what we're calling the retrospective analysis. These are where you have separate studies or separate monitoring events. They can be within the same study where you have workers doing passive, doing an activity and being monitored with passive dosimetry one time and then later, or earlier by quite a lot, being monitored by biological

monitoring. The other approach, another approach you can do is have a surrogate estimate for the passive dosimetry from the PHED and compare those to biomonitoring.

For these comparisons we have the same uncertainties in the passive dosimetry as I mentioned in the concurrent. And then also, you can also, because we're comparing numbers, or exposure estimates that were happening at different times, different study conditions can affect these. For example, different equipment types or differences in personal protective equipment and differences in the product concentrations or the dilute spray concentrations for applicators. There are also uncertainties, biological monitoring that can affect these comparisons.

Unlike the concurrent analysis we don't have the concurrent passive dosimetry so you don't have to worry about interception by the dosimeter, but you have the other factors from, that were, had been listed previously. And then also if they were, again with the, if the passive dosimetry techniques were varied between studies, patches versus whole body dosimeters, those add to the uncertainty of the estimates. And in some cases there are no, the, if the patches for example are on the outside and we use clothing

penetration factors, those add to the uncertainty of the estimates as well.

This is an example of a nonconcurrent monitoring that was conducted in the same, within the same study with fluazifop-butyl, this is from Chester and Hart in 1986 where two separate applications were monitored. The first one was with biomonitoring, they monitored 13 mixer/loader applicators applying this herbicide with vehicle mounted sprayers and each mixer/loader/applicator was monitored, first with biomonitoring where they had 24 hour samples for 2 days pre-exposure and then 7 days post-exposure and then after that 7 days they had another monitoring event where they monitored them with passive dosimetry.

And they compared those, so what you're seeing here, each dot is a single worker and the amount of fluazifop that was recovered from the urine, and fluazifop is a major metabolite from the fluazifop-butyl and then the estimated dermal exposure in milligrams total over the body from the dosimetry. So the r squared, if you correlate those two is fairly good. These are log, a log-log plot of the original numbers that they reported and then which this equation up here is the log transformed, is the regression of the log transformed data.

And again Table 3-2 in the background document, EPA reported comparisons. In this case they used dermal absorption, or I'm sorry, passive dosimetry estimates from the Pesticide Handler Exposure Database, PHED, and in the risk assessments, any biomonitoring used in the risk assessments. So the range of ratios is much larger than in, when we had concurrent monitoring, but half of them were still within an order of magnitude of 1 and that's considered pretty good because of all of the, anytime you're dealing with field studies you have a lot of uncontrolled variables and so there's a lot of variability within studies.

So that to get comparisons that are within an order of magnitude are considered pretty good. So basically in this case most of the passive dosimetry estimates were higher than the biomonitoring, but not all of them.

And so the take home that we, what we took away from that is that while the passive dosimetry didn't consistently estimate, overestimate exposure, they tended to be higher in most of these comparisons, but that they were still fairly close to the biomonitoring estimates in these comparisons.

So in conclusion the comparisons that we did, or that we have reviewed here suggest that we get

either similar or correlated results for both the concurrent studies and the retrospective analyses. In may cases we had insufficient information to do absorbed dose estimates and so we ended with just simply looking at correlations instead. A lot of times we're missing, for example the amount of pesticide that was handled in the study so we can't do an absorbed dose. Or we don't have the information we would need for a full absorbed dose.

Also because of the variability of field studies the results that are differing by less than an order magnitude we would still consider pretty close. And we did see greater differences in the retrospective than in the concurrent monitoring. But what we also felt was that there was not a systematic bias shown in these comparisons.

We didn't have a consistent overestimate with one or the other and in particular we were comfortable that passive dosimetry probably wasn't consistently underestimating exposure which was a concern that we were most concerned about.

Because these methods are coming at it again from the diverse approaches to exposure, we take, we find this is supporting evidence of exposure and that's actually one of the questions you're going to be asked

about and we felt that there wasn't a substantial underestimate of exposure. And that's my last slide. Any questions?

DR. HEERINGA: Thank you very much, Doctor Beauvais. Members of the panel, any questions or points of clarification on Doctor Beauvais' presentation? Doctor Lu?

DR. LU: How do you calculate absorbed dose using biological data?

DR. BEAUVAIS: As in biomonitoring?

DR. LU: Yeah.

DR. BEAUVAIS: First of all you quantitate the residues in the urine and so you say, okay, this is how much, how many milligrams of my metabolite, and that is in sequential sample usually, so we'd say in sequential 24 hour samples I had a total of, you know, so many milligrams in the urine. Then we relate that to, if it's a metabolite, you relate metrically, you say, okay, that, what's because I have this many milligrams I need to convert it to how many milligrams of the parent compound if it's a metabolite.

DR. LU: No, I guess my question is this. Say for example you have seven urine samples

DR. BEAUVAIS: Okay.

DR. LU: on one particular day from

DR. BEAUVAIS: Yes.
DR. LU: particular workers
DR. BEAUVAIS: Yeah.
DR. LU: do you analyze separately? Or do you pool the sample?
DR. BEAUVAIS: They're pooled.
DR. LU: Okay.
DR. BEAUVAIS: The samples are pooled.
DR. LU: So you pool the samples together and you got a number
DR. BEAUVAIS: Yes.
DR. LU: and then you have multiple day results
DR. BEAUVAIS: Yes.
DR. LU: assuming, and then you sum them together?
DR. BEAUVAIS: Yes. So we're getting a summary number at the end.
DR. LU: And normalize by the volume? And then you
DR. BEAUVAIS: Yeah, exactly.
DR. LU: do the calculation.
DR. BEAUVAIS: Yeah.
DR. LU: Okay. Aren't you worried about the volume dilution? Say for example you have seven

urine samples

DR. BEAUVAIS: Uh-huh.

DR. LU: and each gives you 200 microliters, or 500 mil, do you add them up together assuming that each one of them you're analyzing individually

DR. BEAUVAIS: Yes.

DR. LU: they'll come up very close the limit of detection level. And all of a sudden you pull them together because of huge volume

DR. BEAUVAIS: Oh, we

DR. LU: the composite sample becomes non-detect.

MR. DAWSON: Typically you wouldn't pull like if you had a time course where you're measuring, let's say 5 days worth of 24 hour urines, you would analyze each one separately

DR. LU: Right.

MR. DAWSON: and take the

DR. LU: Okay.

MR. DAWSON: the calculated residue from each sample and add it together. And generally the way these studies are done well, it depends upon how you're doing them of course, but let's say it's a single exposure event day that's monitored and then

you're looking at the time course of excretion after that, you would add those all together because it would represent that single day of

DR. LU: Uh-huh.

MR. DAWSON: exposure, even though it took 4 or 5 days or whatever for the residues to completely be excreted.

DR. LU: Okay.

MR. DAWSON: So we want to make sure we capture that.

DR. LU: Okay, good.

DR. HEERINGA: Doctor Hanwerger.

DR. HANDWERGER: As an endocrinologist I frequently rely on urinary excretion of hormones to tell whether patients are in a hyper-secretitory or a hypo-secretitory state and I find the collection of urine to be one of the most frustrating things I have to rely on because the data is invariably poor. It's very hard to get people to collect a 24 hour urine and have consistent 24 hour as judged by something like urinary creatinine.

Do you use a measure of creatinine or something else to really tell you whether this is a 24 hour urine? I can see somebody walking out on a field wearing this space outfit that you have and is not

going to worry so much about, you know, how he's going to collect his urine if the bucket is sitting far away and he's got to go, it's easier to just move over somewhere else in the field and take a leak.

So I would think that 24 hour urine from somebody under those conditions would not be the most reliable and I certainly wouldn't want to make a clinical diagnosis of Cushing's Disease or Addison's Disease based on a 24 urine of somebody out in field spraying pesticides. So I mean I think you, and I'm not surprised that your correlation isn't perfect, I think it's superb considering the fact that there is so much variability. I think so often non-clinicians think that a 24 hour urine is a 24 urine, but it's not.

DR. HEERINGA: Mr. Dawson.

MR. DAWSON: I'm sorry, Jeff Dawson, HED, one comment, we have the same frustration and what we try to do on our protocols is to, A, build in some observational component to make sure, you know, that people are trying to, during the field work and such and some of our recording aspects, but then also look at creatinine and, you know, urine volume outputs, anything we can use to get a handle on the fact that, the completeness of the sample.

DR. HEERINGA: Yes, Cynthia Hines.

DR. HINES: Just a comment on the previous comment and then another question. I'm not sure how other people do their 24 hour urine field study but you raise a good point and what we do in our studies anyway, is we try to make that as easy for the field workers as possible and they actually have urine kits and bottles with them in a convenient portable way so that if they're out in the field and have to take a leak, they don't have to go anywhere to get their bottle, they have it with them.

So I mean your point is well taken, you always never know if you've really got it but we do do the 24 hour creatinine and are trying to check for that. And it's always a worry but we do what we can to make that as easy for the worker as possible.

So, the my other question is, I don't know if you've had a chance to read Richard Fenske's comments yet. He raises a point on the comparison of passive dosimetry and biomonitoring that had occurred to me, and that is, how sensitive is this analysis that you're doing to the choice of the compounds that you have selected here?

Essentially, and when you get a chance to look at this, he breaks down this data into looking at Chlorpyrofos separately from Atrazine. And then there

looks like, and I haven't had a chance to rigorously look at this, but it looks maybe a little more systematic bias may be introduced, that there may be some compound dependent results. So could you perhaps comment on that?

DR. BEAUVAIS: Well that was the intent in looking at a variety of compounds and, yeah, certainly. And in the Tables 3-1 and 3-2 one of the things that EPA was doing when they were looking at these was they were looking at the effect of dermal absorption. In some cases you'll see that in looking at those tables that more than one dermal absorption value is used and just to show, here's what happens to the ration. And basically the ratio is proportional to the amount of dermal absorption. If you assume twice as much absorption your ration doubles.

And, yes, absolutely these ratios are sensitive to all the assumptions that we're making about dermal absorption. And with regard to the passive dosimetry and about the percent metabolite that's recovered, so when I was saying that, you know, 70% of Chlorpyrofos is assumed to be recovered as TCP, because we take that number, they yeah, absolutely. It's compound specific and it is sensitive to the compounds. And the best that we can do is look at a

variety of compounds. Anything to add?

MR. DAWSON: Just one other, Jeff Dawson again, HED, one other comment. When we try to prepare those tables we just tried to capture as much as we could, you know, in the time frame we had to we basically just opened up the cupboard and took what was there. So the lack of a certain chemical whatever, we may not have had the information for a variety of chemicals.

DR. HEERINGA: Doctor Chambers.

DR. CHAMBERS: A couple of questions. The people that are in the moon suits like that that you showed a picture of, are they actually expected to do their normal tasks suited up like that?

DR. BEAUVAIS: Yes.

DR. CHAMBERS: Really?

DR. BEAUVAIS: Yeah. When they're suited up like that, that's because they're applying suited up like that. That moon suit is not the dosimeter, that is actually what they're wearing.

DR. CHAMBERS: Oh, no, no, I know that's not the dosimeter but it just seems like it's awfully cumbersome to do their normal tasks. They can handle that?

DR. BEAUVAIS: Uh-huh.

DR. CHAMBERS: Okay, all right.

DR. BEAUVAIS: Well, and that's when, in yesterday's discussion they were making the point that they want to have, in the AHETF studies they're looking for the minimal toxicity compounds or the or, excuse me, minimal toxicity formulations to work with because they don't want people dressed up in moon suits. And, by yeah, if you're applying something that's terribly toxic you're going to, in some of these OPs you're going to be wearing that stuff.

DR. CHAMBERS: Okay. Another concern that I've had is with the whole body dosimeters, the underwear type thing. The studies that you've looked at that have included that, have there been concurrent urinary samples at the same time? Because it seems like with a whole body dosimeter you're certainly going to get some interception, that's the point of the

DR. BEAUVAIS: Yes.

DR. CHAMBERS: dosimeter.

DR. BEAUVAIS: Yeah, and the way that they get around that is, is the dosimeter is actually acting as another, as a layer of clothing. So they're wearing the t-shirt that is going to be used as a dosimeter in lieu of the t-shirt that they would normally wear. So that essentially it's replacing their clothing instead

of in addition to.

DR. CHAMBERS: But are there studies that are looking at biomonitoring concurrently?

DR. BEAUVAIS: Yeah.

DR. CHAMBERS: Because those would necessarily, the urine samples necessarily would have less there because you know you're intercepting some from the

DR. BEAUVAIS: Yes and --

DR. CHAMBERS: dosimeter.

DR. BEAUVAIS: and what, and our assumption that we're using in those is that whether it was intercepted by the dosimeter is what the person's clothing would normally intercept.

DR. CHAMBERS: So you're adjusting?

DR. BEAUVAIS: No, we're let's see how to

DR. CHAMBERS: Are you adding that amount to the urine then to try to come up with a total

DR. BEAUVAIS: No.

DR. CHAMBERS: total body dose?

DR. BEAUVAIS: Okay. I can tell you that we're not and, because we're assuming it wasn't absorbed. Again it, because the person is, if the

person weren't wearing the t-shirt that was being used as a dosimeter they would be wearing a different t-shirt, so that dose would not be absorbed because of the clothing, it would be trapped in the clothing.

DR. CHAMBERS: So the whole body dosimeter is not an additional layer of clothing then?

DR. BEAUVAIS: No, that's

DR. CHAMBERS: I thought it was.

DR. BEAUVAIS: yeah, exactly. In these concurrent studies that's what they're

DR. CHAMBERS: It's not an

DR. BEAUVAIS: that's how they yes.

DR. CHAMBERS: And the other concern that I've had for many years with these kinds of studies as well as with the residentials from surfaces and so forth is, does anybody every monitor how much of the breakdown products are out there on the skin that are actually just passing through into the urine? You know, certainly where the organophosphates

DR. BEAUVAIS: Uh-huh.

DR. CHAMBERS: the breakdown products, TCP or whatever, that's going to be the same thing breaking down in the environment as is showing up in the urine through metabolism.

DR. BEAUVAIS: Uh-huh.

DR. CHAMBERS: And so are you getting some urinary metabolite presumably that's really nothing more than an environmental breakdown product passing through?

DR. BEAUVAIS: Yeah, and that's actually, there are a couple of recent studies that have looked at that and, yeah, found that there is some of that happening. But I'd say probably not a lot. But again that's going to be compound specific. But yes, that is an issue that people are aware of and that there is actually studies where they're trying to investigate that.

DR. HEERINGA: Doctor Portier and then Doctor Appleton.

DR. PORTIER: I was looking at your figures on slides 22 and 23 and trying to understand what the arrow bars, I mean it says standard deviation, that means that for each of these handler tasks there's multiple people that did concurrent sampling. Is that what that means?

DR. BEAUVAIS: Yes. Yeah, so these are the geometric mean of individual results, yes.

DR. PORTIER: Okay. It would have been better if you plotted the differences, right? Because of, between the

DR. BEAUVAIS: Yes.

DR. PORTIER: between the concurrent estimate and the biomonitoring estimate, so I could

DR. BEAUVAIS: Okay.

DR. PORTIER: figure out what the real variability, and the uncertainty on the difference is what I'm more interested in than the differences of the means. It's just a minor point that would

DR. BEAUVAIS: Okay.

DR. PORTIER: have helped. Especially on that slide where you're trying to figure out for situation 3, whether that's really different or not.

DR. BEAUVAIS: Uh-huh, okay.

DR. HEERINGA: Doctor Appleton.

DR. APPLETON: Yeah, I gather you're still using DPR and I address this to the EPA colleagues as well. You're using fixed values for dermal absorption

DR. BEAUVAIS: Yes.

DR. APPLETON: exclusively to go from passive dosimetry for externally deposited residue and there's no

MR. DAWSON: Yes, that's correct. We're still using

DR. APPLETON: there's no temporal

input.

MR. DAWSON: No, we have

DR. APPLETON: So you're sticking with saturation.

MR. DAWSON: we're still that's correct.

DR. APPLETON: Okay, I was going to talk more about that this afternoon for data needs but I just wanted to confirm that. Thank you.

DR. HEERINGA: Steve Heeringa. I have a question to follow up on Ken's question on slide number 22. There's sort of a remarkable correspondence between the means on the passive dosimetry and the biomonitoring. There's a transfer coefficient in the absorption under the passive dosimetry or does that not factor in here? In other words did you have to calibrate these two graphs by choosing a transfer coefficient to get the same?

DR. BEAUVAIS: No, no, the

DR. HEERINGA: You just chose a constant and it worked out so these things map onto each that closely?

DR. BEAUVAIS: Yeah, these, for handler exposures we don't have transfer coefficients and these are the amount that's absorbed on the dosimeter while

the person is spraying or mixing and loading. Transfer coefficients are used in reentry exposure, or is that

DR. HEERINGA: No, I mean the dermal transfer across skin, through skin transfer.

DR. BEAUVAIS: Oh, oh, I see what you're saying, yes. So, oh, so the question is

DR. HEERINGA: Absorption.

DR. BEAUVAIS: are they coming from the same study, is that

DR. HEERINGA: No, did you have to

DR. BEAUVAIS: Yes, oh there's

DR. HEERINGA: Those range of values

DR. BEAUVAIS: These, okay.

DR. HEERINGA: 2% to 10%, did you have to calibrate that value to get these two curves to correspond that closely?

DR. BEAUVAIS: Just a second, we're yeah, Tim Leighton can answer that.

DR. HEERINGA: Sure, Doctor Leighton.

DR. LEIGHTON: Although this seems to be a lifetime ago and I'm in a different job now, when we worked on this we used a 3% dermal absorption.

DR. HEERINGA: Okay.

DR. LEIGHTON: As a constant.

DR. HEERINGA: You just chose a constant

and

DR. LEIGHTON: That's right.

DR. HEERINGA: which is good. Thank you very much, Doctor Leighton.

DR. LU: 3% across all the pesticides.

DR. LEIGHTON: For Chlorpyrofos.

DR. LU: How about Atrazine?

DR. LEIGHTON: That one I'm not sure of.

MR. DAWSON: Jeff Dawson again. What we would do in these cases is for all the variety of chemicals in the risk assessments we would have taken the dermal absorption factor specific to that chemical and they could have been derived from a variety of things but most of the time they're, you know, dermal absorption studies.

DR. LU: Yeah, as I recall there is a table in the document that shows different absorption for different pesticides, right? Like 24D and

MR. DAWSON: Right.

DR. LU: Okay.

DR. HEERINGA: Thank you very much. It just sort of struck me that several of these points lined up nicely and I think a typical trip, given you have a component like that is to essentially calibrate these variables until you get sort of a maximum overlap

at several points.

Yes, Doctor Bucher.

DR. BUCHER: So I'm not an expert in this area at all so I can ask a very naive question. I thought I understood what was going on now and I'm confused about something and that is the fact that with these whole body exposure suits, if they are in fact simply replacing the clothing that they would normally wear, how is what is absorbed on those whole body patches related to what is absorbed, what is available for absorption on the skin?

DR. BEAUVAIS: Yeah, that's actually one of the questions, one of the reasons why we have questions, or one of the uncertainties related to passive dosimetry, because at the same time that it's serving that purpose it's also serving as a surrogate skin. And in the case where the dosimeter is below the clothing, then that, it is serving as a surrogate skin. If you have a dosimeter that's outside the clothing you're using a clothing penetration factor. And, yeah?

DR. BUCHER: So I would think that either one of those situations would be better than using it to replace normal clothing.

MR. DAWSON: One clarification. For most of these kinds of studies for occupational studies, the

dosimeter would be placed between what an individual would normally wear as their clothing and their skin. So it would be intercepting the residues after it would pass through their particular normal work clothing before it deposited on the skin.

DR. HEERINGA: Yes, Doctor Hughes.

DR. HUGHES: One quick question which is a follow up. With regard to environmental breakdown products that might interfere with the dosimetry analysis, you did a collection beforehand. And did you actually eliminate subjects that might have sprayed recently? Was that an assessment of what they might have picked up in the environment or was that an assessment of what they might have sprayed in an instance or event that occurred previous to your monitoring event?

DR. BEAUVAIS: Well these are a correlation of studies that other people were doing and in general when, I would say that in general you'd probably want to eliminate that person. But I've also seen studies where they simply report that, you know, this one was high going into it.

DR. HEERINGA: Time for a few more questions before we Doctor MacDonald.

DR. MACDONALD: Yeah, my concerns are very

much like Doctor Bucher's, that just the relationship between the normal work clothing and the clothing worn during the study and so on. At one point I thought well if you put everything on the outside you're measuring the exposure of a worker who worked naked and then you would have to interpret that for an actual scenario by putting clothing on and determining how much it's keeping out. And there's something about the, some of the case studies that are being done, it seems to be the way you're doing it.

But I also would like some clarification as to how the pesticides are actually getting in. Is the major source through the protective clothing or normal work clothing or are there also exposed areas like the back of the neck or face and so on, and in fact most of the pesticide is getting in through the small exposed areas? Do we know this?

MR. DAWSON: Jeff Dawson, HED, it's very scenario dependent, so depending on the activity. For example if you consider let's say a mixing/loading activity where, you know, you're doing a lot of this stuff right in front of you it could be around the seams of the shirt and that area, it could be actually, if it's loaded enough it could actually penetrate through the fabric, it could go through the buttonholes

and such of the garment. If you're doing a, let's say a different activity such as air blast applications we tend to see, and this is borne out in the data, where a lot of the residues are on the, you know, the back of the head and the back itself and such.

So that's why we're, we talked to someone yesterday about like segmenting the whole body dosimeters and collecting patches from different regions. We're interested in understanding the total loading for the individuals, but also how the loading occurs and it gives us better insights into how we might manage those exposure levels.

DR. MACDONALD: Yeah, just to follow up too, just looking, the pictures have really helped but I could see that, I would expect a tremendous amount of variability between workers, just in the way they put their clothing on, the kind of clothing available to them, and with certain especially where you don't have machines and pumps and so on, just how clumsy they are in handling the product. So I would certainly expect some scenarios to have extremely high worker to worker variation or even a high variation in applications within the same worker.

And just a related matter too, it's not clear how much information you have on variability within

worker doing essentially the same task under the same conditions.

MS. DAVIS: Absolutely we have the same concerns and inherent in the data there is extensive variability. And actually we're going to be talking about the inter and intra-variability in one of the charge questions later this week because it is an issue for us, right.

DR. HEERINGA: Okay, thank you everyone. We'll have a chance to return to this general topic I think later in the morning when the Agricultural Handlers Task Force does their presentation as well.

But at this point I think on the agenda we're scheduled for Jeff Dawson and Jeff Evans of Health Effects Division to do a presentation on methods for handling, for measuring hand exposures.

MR. EVANS: Thank you very much, Doctor Heeringa. My name is Jeff Evans of the Health Effects Division. I'd also like to have Phillip Villanueva join us for any statistical questions that may arise from this disucssion.

As you probably gather from the background and our discussions and comments, that the hand rinse versus cotton glove performance issue is very important to us with respect to developing generic databases. So

if we could approach this program with starting simple and getting more complicated as we get through this.

The current approach of course is the most simple and our mechanistic analysis is another kind way of saying, whatever we could find from the available literature and I do this with some trepidation knowing that some authors are present on this panel and I apologize in advance for any misinterpretations. Also I did try to faithfully in the background document reproduce what I had found in those papers and again I apologize if there is any inconsistencies in the, in what I put in those tables and if I captured your information correctly.

And the finally we're going to also look at the performance or comparisons of measurements in the data in PHED using the case studies that Jeff Dawson described yesterday. So we're going to certainly look at what we have now to approach this issue. And of course this augments our discussions with respect to biological monitoring and passive dosimetry comparisons overall as Sheryl presented this morning and the task force will address this afternoon.

So our current practice as I pointed out is very simple. We're just assuming that the two are interchangeable and we have to date not made any

corrections based on methods within the Pesticide Handlers Exposure Database.

So again our analysis of the literature, we certainly came away with I think several is a charitable way to put all the variables and factors that impact what you may be measuring on hands to consider. There's a number of different study design issues that complicate matters. We have test tube grabs, some of a mass balance approach and other methods, you know, spiking skins of individuals who are in vitro, porcine skin. So, and I think it's important to point out that there has not to date been a comprehensive study that really looks at this sort of holistically. And so we're relying on what's available in the literature and what we have in PHED at the moment. Next slide please.

So, to start off I think the seminal paper that addresses this and probably got everybody going on the relative comparison, was Davis back in 1983. He reported that hand measurements based on the use of cotton gloves to be considerably higher than hand measures using ethanol rinses and this was apple thinners reentering field treated with azinphos-methyl. Richard Fenske a few years later also reported measurements with gloves to be higher at short

monitoring periods, 1 and .5 hours and also at, these began to notice smaller differences observed when the monitoring periods were longer and this one 1.5 to 3 hours, so the differences started to diminish somewhat as the monitoring period increased. He also noted some breakthrough of the lightweight cotton gloves which may have certainly impacted the results and had speculated that in the Davis study they may have used a heavier weight cotton gloves. So there are always, there's always something complicating, you know, a very simple read for a regulatory scientist. So Fenske has looked at this issue quite a bit. And another study reported hand measurements again for workers reentry fields treated with azinphos-methyl and thinning apples, that cotton gloves were 3.5 times the measurements using hand rinses. And again I think I should not that the apple thinners were monitored for two hours and I think this is where, you know, we have certainly got the notion of perhaps making some sort of correction factor for the hand rinse method from this paper where he had had a hand rinse correction factor from a compound having a similar LOGKOW to account for perhaps losses from the hand rinse method.

And in the next slide you'll see some summaries from those data. There's the original study

looking at the differences in the hours and that certainly got us thinking about exposure duration and other literature studies also seem to hint at that possibility.

And then in the table below is the azinphos-methyl study where he had gloves and washes. That 68% is based on a correction from captan, with captan and azinphos having similar chemical properties. I also included the wipe there, you know, Richard has pointed out many times that the wipe method is a very poor performer and I think it was mentioned yesterday in one of the public comments, that the wipe is also a very performance issue.

I don't know of any studies conducted by any task forces or signatory to our agency for occupational exposures where they relied on the wipe for measuring hands. I do know that this wipe is used for the face and neck and so I think that certainly has some impact on our thoughts regarding that method for the face and neck wipes. Next slide please.

So I probably should have stopped there because that certainly gave me a nice handy way to proceed with correcting for hand rinses and perhaps solving a problem, but the more you read, the more complicated it seemed to us and the more things entered

the picture. Certainly as investigators we're interested in different items of concern.

So to summarize some of the things that struck us on these data was that when you're looking at hand rinse performance, certainly the physical chemical properties of the pesticide, its solubility, optimal water partition coefficient strikes us as very important. Also perhaps molecular weight. Some of them also looked at the residence time on skin, acknowledging the differences in logistical considerations of field studies. So you might have some subjects waiting for periods of time and that might impact on that performance so they incorporated immediate rinsing and perhaps waiting periods of up to an hour.

Over the years, perhaps based on chemical performance methods, investigators selected alcohols and soap and water so there's a wide variety of solvents that have been used in these hand rinses. Concentration appears to have some impact on removal. As you have additional layering on the skin maybe it becomes easier to remove as you have more on the skin, that first little bit being absorbed and perhaps tying up that mechanism. The duration of exposure of the monitoring period also as we saw earlier in the

presentation, that might have some impact on the performance of hand rinses, whether it was a short or a long period of duration. And the nature of the residue I think is something that we may to also consider since we have several task forces and several different concerns.

We have exposure to different types of residues for reentry into pesticide treated fields. The residues may be more complex. They're complicated by being bound with soil or plant waxes and plant uses and other articles. When you have sprayers they're primarily exposed to a dilute concentration that's perhaps more uniformly spread over the body. And then you have mixer/loaders that are exposed to concentrates, getting concentrated splashes. So there's certainly a lot more going on than in my simplistically evaluated, or simple algorithms. But of course once again, the more you look at it the more complicated it got and I certainly wish I'd stopped at the first two studies, but I didn't.

So just some additional comments on some of those items I highlighted previously. The physical chemical properties of the pesticide and we really do think indeed if it is determined that it's important to correct for hand rinse performance, that we really do

think that looking at a physical chemical with properties of the surrogate compounds is a very important and perhaps a practical solution for a regulatory solution.

The performance in the hand rinse efficiencies have been reported in a number of studies. Richard Fenske and his colleague in Washington at the time, Alex Lu and Brian Curwin looked at some field reentry studies and tobacco fields treated with a water soluble compound and Campbell looked at the performance of different solvents on chemicals having very different water solubilities on the porcine skin.

And again I think that these studies I think can give us some of the basis for thinking about making the corrections. They do contain a lot of these surrogate chemicals that are used in generic database studies. And, you know, we had started to put together some regression equations comparing solubility, and the measurements of those, we just didn't have time to do that for this presentation but it's some we are certainly thinking about. And one of our colleagues at PMRA also thought that dermal absorption studies where they measure wash off after certain durations might also be an important component to consider in that analysis.

Of course performing these studies is a very difficult and maddening affair at times as pointed out by some of the panel members this morning and certainly that's not to be underestimated. And in doing so many of the investigators did incorporate a waiting period of sometimes an hour or 90 minutes, something like that. And others were able to capture the residues immediately after the exposure, particularly the test tube grabs where they had more of a mass balance approach. And in general, not always, but in general it seemed to us that the longer the waiting period the lower the rinse efficiency. So that would certainly be a study design consideration from our perspective and I certainly prevail upon the task forces to include a collection time of hand rinses immediately upon returning of the subjects from the field or study site. Next slide please.

The impact of the rinsing solutions, we have seen in a lot of the studies presented already, and we'll see certainly more later in this presentation where there is a wide variety of solutions that have been selected. Again, a lot of it might have to do with the thoughts about the method validation for the hand rinse. However, it should be noted that the soap and water solutions are currently used by all the task

forces, that does seem to be the preference. I had read in some of the literature that there were concerns for the subjects of the studies using, oh, I don't know, 50% methanol might be an issue deliquifying those hands after awhile, it may be enhancing the absorption of the pesticides that they were exposed to in that study. So for a variety of reasons it seems as though the state of the art as it were has focused on the use of more soap and water oriented washes.

And so I think the key studies that sort of address the different kinds of rinse efficiencies was the Brewer which was a compilation of many studies where they spiked hands of different solutions of many different pesticides, some of which are surrogate compounds. And those also include the Fenske and Lu data.

The 22% value you see there is for chlorpyrofos and I always think about that when I look at some of those chlorpyrofos biological monitoring studies. Perhaps, and I'm speculating here out loud, that, you know, in the mixer/loader/applicator ones where there are gloves it might not have been as much of an issue, but if you have reentry exposed to chlorpyrofos residues and you're having a poor performance, that might explain some of the differences

seen in the reentry compared to the mixer/loader. I'm simply speculating here but just some food for thought.

In the compilation study discussed in Brewer there was a high range, all the way up to 96% with a mean of 73% reported. In the study where they looked at the spiked porcine skin, the Propinyl certainly performed the best but I was struck by the fact that the soap and water rinses were the most consistent for this wide range of chemicals. That actually was the tightest range of percents. And I think both of the papers provided clues regarding the impact of skin concentration. Most definitely the Campbell asserted so and I think the Brewer paper was not as, it didn't seem as clear to us as we had read through that, Propoxur being the curious one in there. Next slide please.

So again as I pointed out Campbell saw definitely an increased efficiency with higher concentrations on the skin and again the Brewer study presented a little more mixed results.

And once again, bless them all, the study investigators used different solvents, different procedures, have different views on capturing and perhaps that may have complicated some of the results presented in that paper.

When we looked at studies that really focused on reentry, again having longer durations, it does seem that there is the potential for equilibrium or perhaps some layering going on as you have long exposure durations and you can mitigate perhaps some of the concerns about losses due to binding of the skin or absorption by having a longer study, and thus you may have a layering effect or some kind of equilibrium going on.

So that studies that may be conducted for short durations might overestimate exposures for maybe 8 or 10 hour periods. It's a two way street and so the values from an 8 or 10 hour study may actually underestimate an exposure scenario where you're looking at a 1 or 2 hour exposure. So it does seem to be a complicated matter to us. Slide please.

And these studies that look at longer term contact with residues, at least as far as I was able to tell, were largely studies looking at reentry exposure. And again that's where you have maybe a more complicated residue pattern being developed because of the other active soil and plant waxes and the like.

So in Fenske in early '89 we began to see perhaps a difference between short and long durations. Derkin out of Syracuse looked at some earlier reentry

studies and compared the concentration of the residues on the leaves to the concentration of the residues on the hands, making some assumptions about the surface area of the hand and established a fairly nice relationship between the DFR, which is measured in micrograms per square centimeter and then the micrograms per square centimeter captured on the hands of the reentry workers. Of course in those studies there was gloves and hand rinses so we thank them for that.

Spencer I think also had a very nice analysis of the differences between long and short durations and again described that loading seen in the first two hours. And I think that's a really important thing to consider in a study for a number of reasons. One is for the handler studies the detection issue and then making sure that we get good measurements on the hands. And, you know, it suggests to us that maybe there is some concept in some of the situations, particularly reentry, where there may be equilibrium established after repeated contacts. And so longer study exposure durations are important in field study designs. Next slide please.

And some final thoughts, at least from, you know, our read of these studies, Jeff's going to get

into a few more after he looks at the case study data, but it seems to us worth considering some sort of relationship anyway between the efficiencies that are reported in studies, perhaps considering laboratory penetration studies, some sort of relationship between physical chemical properties and the rinse efficiencies that have been reported.

To play the devil's advocate with the task forces which I enjoy doing, as part of a field study design, perhaps select a surrogate chemical with a known and reliable biomarker and adding any remaining residues based on what is found in the urine. Maybe making adjustments for inhalation. You know, we have a lot of thoughts about comparing biological monitoring and the impact of the whole body dosimetry. I mean ideally you would have a study maybe collecting measurements with patches but if indeed the methods are capturing everything, then whatever you do collect in urine should either be small or be of low significance to your final unit exposure estimate.

And as some might conclude, make not adjustments at all to these surrogate data based on the conclusions of the passive dosimetry and biological monitoring comparisons.

And with that I'll hand it off to Jeff Dawson

who's going to describe additional analysis with the data in the PHED.

DR. HEERINGA: Thank you. Mr. Dawson we're at about 10:05. I don't want to rush your presentation. I think what I, my view is we'll go ahead with your presentation. We may have to take a break right after your presentation before you take questions if that's okay with you. Please proceed.

MR. DAWSON: Thank you. I'm just going to introduce the summary of the data and then I'm going to pass it over to Doctor Phillip Villanueva who dealt with the analysis of these data so I'll only talk for a couple of slides.

So basically yesterday I introduced the case study information for the six scenarios from PHED and our thought was, in addition to the analyses that Jeff just described, why not also take a look at the actual field monitoring data that we had to see how these methods have performed under field conditions.

So basically what this slide shows is the distribution of the different types of data that we had to work with based on what was in the case study. And so across the y axis here is just the number of data points that we have and the x axis here is just the varying combinations of sampling methodologies and

whether or not the monitored individuals were wearing protective gloves of some sort. So the blue bars here represent those individuals who were working with bare hands and then the red bars represent individuals who were wearing some sort of protective glove over the top of their hands.

And then each of the bars represents, well, and then the varying bars across the bottom represent the various sampling methodologies. For example, in the first bar right here the hand sampling was done with an acetone wash, straight acetone. In that one they were wearing protective gloves. In this one here the individuals were barehanded but they were, the sampling was done by collecting it with a soap solution. This bar here again was also a soap solution but in that case the individuals were also wearing a protective glove to reduce the exposures.

So from the case study this was essentially totaled up to 513 data points and there are 12 different combinations of sampling methods and whether or not they wore protective gloves.

And then basically this slide just represents those data points and the code kind of carries through here, the various combinations of the sampling media and whether or not they were barehanded or wore

protective gloves. And on the x axis here you have the total amount of active ingredient that they handled and here was the total amount of residues in micrograms that were measured on those hands. And keep in mind this is for the 6 case study scenario so it's mixing, loading and applicators and it's different forms of pesticide.

So in some cases for the applicators it would be a dilute spray but, and for the let's say people loading granules it would be a, you know, a concentrated solid material so all the variety of pesticide antagonists or whatever you want to call it is also reflected in this slide.

And then on this slide, just to show how once you start segmenting the data down based on different scenarios and such, how you reduce the number. So, and this particular slide represents applicators who were wearing protective gloves and you can see instead of the 12 different combinations all of a sudden you're down to 4 different combinations. This is the soap solution where they were wearing a protective glove and ethanol with a protective glove and cotton gloves as a sampler with a protective glove over that and then isopropenyl. And here you, just by segmenting the database on whether or not they were a mixer, loader or

an applicator and whether or not they wore protective gloves, you go from 513 data points to 73.

So we did a series of analyses based on this and what I'd like to do is to hand the presentation over to Doctor Phillip Villanueva who actually did that part of the analyses.

MR. VILLANUEVA: Just a quick clarification, Mr. Villanueva, I'm not a doctor, but thanks.

So anyways we're, if we can go back to the previous slide I just want to talk a little bit about that.

So Jeff's team, one of the questions they had was, do certain hand monitoring methods result in consistently better recoveries? In other words, are the unit exposure values consistently higher? Depending on whether it's a removal or a trapping, so whichever type of hand monitoring method we're talking about. Next slide.

So we looked at various scenarios, 6 in total so there were applicators versus mixer/loaders, solid versus liquid formulation and then of course as Jeff just mentioned, protective glove versus bare hands. So we looked at each one of these 6 scenarios separately, ensuring that we had comparable unit exposure values.

And again the goal was just to determine if some of these different hand monitoring methods that we have consistently produced higher unit exposure values across these 6 different scenarios.

Again we segmented the data into 4 different categories for the hand monitoring methods. Some of them being trappings, others being removal. Cotton gloves, then soap solutions and then various alcohols and acetone and then the tie back gloves and other types of hand monitoring methods.

So initially this was meant to be an exploratory analysis, just kind of getting a feel for the data, just a simple Anova approach was performed on the log of the unit exposure values and there are couple of assumptions, a couple of underlying assumptions whenever you're performing this type of analysis.

In this case the log transform data are normally distributed is one of the assumptions. So whatever transform you have to use but basically you want to convert the data and make it's normally distributed before analyzing it. Also, the different group variances are equal, and that's one of the underlying assumptions so that's something we need to check later on also. And the observations are

independent so there's not going to be any type of correlation between the monitoring units, which of course I think you've guessed from some of the previous presentations that that's not the case.

But part of this, in addition to the Anova was a graphical evaluation of the data. So just looking at scatter plots and the probability plots give us a good idea if the data is lognormally distributed or if the variances are approximately equal and just an idea of where the group means lie in relation to one another.

So this is just one of the examples, this is the one I believe was included in the document submitted to the panel members. Again we did all 6 different scenarios. In some cases the sample sizes were kind of small. I'm just going to spend a little bit of time explaining this graph. In each one of these cases again we have the different hand monitoring methods here.

In some cases not all 4 were available, depending on the exact scenario. In this case these were applicators wearing protective gloves with liquid sprays. So here in this case we have cotton, soap and wash and also the symbols here represent different studies so these are the monitoring units within each

individual study. So for these scatter plots you can already see that there's some evidence that there's quite a bit of clustering. So in this case what we have would be the, within study variability, I'm sorry, the within study, I'm sorry, yeah, the, with, in this case we'd have a correlation between the within study samples.

So here you can see they are tending to clump up here so that's already kind of undermining the assumption that the samples are independently sampled. And again, we don't take that into account with a simple Anova analysis. So you have some monitoring units down here so keep in mind some of these may, in some cases may be individuals monitored multiple times. In other studies they might have distinct individuals for each monitoring unit.

Over here we have the probability plots and this gives us a good idea of the, of whether our assumption or normality is being met. Again this is a log scale, we're looking at the los of the unit exposure value, so looking at this normal probability plot is the same as assessing the appropriateness of the lognormality assumption for the original data.

So here you can see with the points lying on these lines here that the assumption of lognormality is

met. You could also do, instead of a visual inspection of that there are statistics that you can use such as the Shapiro-Wilkes to determine if that assumption is being met. But generally what we saw in all 6 cases, and I'll summarize from this later on also, is that that assumption seemed to hold so log transforming the data effectively converted the unit exposure values to normal distributions.

Another nice handy feature of these probability plots is that you can also assess whether or not the group variances are approximately equal. So in this case the slopes of these lines are an indication of the variability in the data, so if they're approximately parallel then you can say that the group variances are equal.

So it seems to be the case for these two groups right here, but not the case here for a wash, there seems to be a smaller variability in that case or a less steep slope. And so again, keep in mind that was another underlying assumption of a simple Anova approach. So I think that's all I wanted to say about that slide, yeah.

As I mentioned before, we looked at 6 separate scenarios, this is just a summary of the one way Anova approach here and we have the different, this

is a sample size for the monitoring units. Again, keep in mind that some individuals were monitored multiple times depending on the study. And then in some cases we have some very small sample sizes so you have to be very cautious about, well, in addition to the assumptions that are violated you also have to be cautious about the sample sizes we're considering.

And these are the hand monitoring methods that are available for these various scenarios. And just a quick look at the significant differences that we saw here. In some cases you'd have cotton being less than wash, in other cases it would be larger, the unit exposure values are, rather the logs of the unit exposure values. So there weren't any consistent results but again this was exploratory, keeping in mind that there are certain assumptions in using this type of approach that are being violated.

And just a quick summary of all 6 of these different scenarios. As I mentioned previously, log transforming the data effectively converted those to normal distributions. I hate to use the term normalize, we tend to use that a lot with this group for different things. So instead I say convert to, convert the data to normal distributions effectively.

Generally there was at least one group

variance that was not equal to the others when looking at these 6 different scenarios, so that was a problem as far as interpreting the results of an Anova analysis. And of course the sample were not independent because of the study design. Basically we expect studies, measurements from within the same studies to be more similar than methods from different studies. So that's a violation of the independence.

So two of the primary assumptions of this type of approach have been violated but the scatter plots do indicate that the study to study variation is greater than the method to method variation, which would imply that basically we would have to find much larger differences than we've observed so far to conclude that certain hand monitoring methods perform better than others. And then of course that wasn't the only goal, we still to determine if one consistently outperforms others. But basically just based on this simple approach it seems obviously that there's no method that consistently results in higher unit exposure values.

As far as possible future analytical approaches, we know there are better methods available out there to take into account these unequal group variances and also the types of non-independence that

we're seeing with these measurements. Some of the approaches we're talking about would be nested Anova which you consider as a subset of a mixed linear model approach.

These, as I mentioned can appropriately model the nesting that we're seeing with the measurements. For instance, you'd want to consider the nesting of measurements within workers so some workers being sampled times and then the workers within the studies. And also again the unequal variance can be modeled more appropriately. We do have some preliminary results from running hierarchical linear models or HLM that we've had time to do between the time of finalizing the document and preparing for this SAP. And we think that, even though I'm going to provide some of the preliminary results, there are even further refinements we can do using such an approach, using HLM.

We can include dummy variables or additional covariates, if we were to use the KOW and consider interaction terms. So we can more appropriately take into account some of the physical chemical properties instead of repeatedly sub-setting the data.

And this is just a comparison of the results I showed earlier from our one way Anova and then the results from the HLM analysis. Again some of this, we

don't see anything here that conflicts with what we saw with the one way Anova, but as I mentioned before, since some of these differences between the hand monitoring methods aren't very large, then some of the significant differences we saw on the one way Anova don't hold when we look at a more complex model that appropriately considers the nesting and unequal variance that we've observed in the data. But again, even based on the significant differences that we do find there doesn't seem to be any significant results, I'm sorry, any consistent results that we see from one scenario to the next. And again many of the significant differences that we saw on the one way Anova don't hold for this type of more appropriate approach to looking at the data. I think that's it.

MR. DAWSON: And then just to wrap things up, kind of where we are in conclusion with this presentation is that we're left with basically two options. One is to adjust the results or not and basically a couple of options we thought of, to possibly adjust the results we're looking at log KOW, adjustments based on log KOW or other physical chemical properties or, depending upon, you know, what the outcome is, is to the comparison of, or biomonitoring analysis that we talked about earlier, maybe adjust

based on that. And conversely, not adjusting hand measurements, again depending upon the biological monitoring analysis and the passive dosimetry comparison we talked about earlier and also the results of this field performance analysis that we just talked about.

And I think as Jeff Evans alluded to earlier, some kind of controlled designed experiment to better specifically address this issue would also be very useful.

DR. HEERINGA: Thank you very much for these presentations. We're at about 22 minutes after 10:00 and I think it's about time that we should take a break. But are there any pressing questions? I'll return after the break, but any pressing questions that anyone would like to ask before we move to a break here with regard to this presentation?

Okay, I guess we'll have a little time over the break to consider any questions.

For the next presenters, which I think are the AG. Exposure Task Force Group, we'll probably allow 15 to 20 minutes for questions after the break so we'll get a little bit later start than the agenda shows, but let's plan to reconvene here at 20 minutes of 11:00 please.

(WHEREUPON, there was a recess).

DR. HEERINGA: Okay, welcome back everybody to the second half of our second morning session of the FIFRA Science Advisory Panel meetings on the topic of Review of Worker Exposure Assessment Methods.

We've just completed a presentation by Jeff Evans and Jeff Dawson and Mr. Villanueva regarding the Agency methods for hand exposure assessments. And before we move on to the next scheduled presentation I'd like to give the panel an opportunity for a few clarifying questions on this presentation.

Are there any questions that the panel has on the material that Jeff Evans or Jeff Dawson or Mr. Villanueva presented? Yes, Doctor Bucher.

DR. BUCHER: This question really isn't specifically related to what you presented but I'm curious as to the relationship between the questions you're raising about how you would possibly utilize information from the existing database in relation to the rest of the context of this meeting about the future studies that are being put together. Is there a relationship between these or are you simply asking for the panel to respond to you about how you might retrospectively utilize the data that you already have

in a better way?

MR. EVANS: You know, certainly we would like both, but for this presentation this really has view towards how we would collect new data if we needed it, and I think also to help us make sense of what we do have since we have a mixture of methods for assessing that part of the body.

DR. HEERINGA: Doctor Johnson.

DR. JOHNSON: Yes. Have you looked at the correlations that might exist between the different measurements that you might have on the same individual? For example, how does the head and neck wipes correlate with the hand washing, how do those correlate with the patches, how do they correlate with the whole body dosimeter, et cetera?

MR. VILLANUEVA: No, I don't think we've specifically looked at how different measurements correlate within an individual measurement, within an individual that's been measured.

DR. HEERINGA: Do Lu.

DR. LU: Just a clarification question. How does the Agency define exposure versus dose?

MR. DAWSON: I guess the standard answer would be, based on what we have, what are included in the Agency wide Exposure Assessment Guidelines. So the

definition there of exposure would be, you know, what's deposited on the surface of the skin. Also, if you read that document it uses the term, and we kind of use it interchangeably, there's a little nuance to it but potential dose and then absorbed dose would be after it passes through the barrier.

DR. LU: And do you think it is adequate to say for example, dermal exposures? There is many ways to assess dermal exposures. And then you multiply by 3% in the case for chlorpyrofos and that number represents dose.

MR. DAWSON: That's correct, so in that particular case we would have calculated an absorbed dose estimate for the eventual calculation of a risk estimate. But how we do it varies depending upon the nature of the hazard information we have available. For example, in recent times, essentially what's been done related to these risk assessments is that large numbers of dermal administration toxicity studies have been developed, so there, instead of calculating absorbed dose estimates we would be using exposure estimates directly.

DR. LU: Right but I guess the question will be for me, is kind of looking at those data, the comparison that you presented in the last two hours,

are those numbers being calculated this way, that, the exposure amount times a certain fraction of the quotient and that resulting number will become dose and being manipulated in all the comparisons?

MR. DAWSON: Right, from the passive dosimetry estimates, that's how we'd be getting it.

DR. LU: All right. Thank you.

DR. HEERINGA: Cynthia Hines.

DR. HINES: Just one quick clarification. When you're presenting isoprophyl alcohol data and ethanol data, is that 100%, is that 10%, is there any water in those?

MR. DAWSON: Several of them were 100%, there were a few that were 50/50. I'd have to go back and look at the exact detail. Some of it exactly wasn't clear from the studies so it would

DR. HINES: Yeah, I might suggest some caution in combining handwash that may come from a straight ethanol or IPA with that that has a substantial amount of water in it because they will behave differently.

MR. DAWSON: Absolutely.

DR. HEERINGA: Yes, Doctor Kim.

DR. KIM: Just a follow up to that. I have a question about whether you're interested in, or

concerned about chemicals that are absorbed inside the skin and the date of that, so the time force behavior of chemicals that are inside the stratocore or in deeper layers of the skin? Because the effect of different washes can affect how that, affect the behavior of those chemicals, they may penetrate further or they may be, they may come to the surface of the skin, et cetera. So that would affect your internal dose estimates.

DR. HEERINGA: Presumably we'll have an opportunity to cover that in more detail as we get into responses. Doctor Popendorf.

DR. POPENDORF: Yes, I just I guess want to follow up on that too because I think the question was really, are you using the data or the data that you presented, was that exposure or dose? And my understanding was that you were presenting exposure without any adjustment for absorption. You'd eventually use it that way but that's not what you presented. Is that not correct or which is correct?

MR. DAWSON: On the hand data from the case study that I presented it's pure exposure, no adjustment for absorption in that. I'm sorry if there was a little bit of misleading with the conversation with Doctor Lu earlier.

DR. HEERINGA: Doctor Bucher.

DR. BUCHER: Sorry, I guess I'm again confused then because it seems to me like if you're going to be adjusting the handwash information for exposure based on KOW for example, that to ignore the possibility of utilizing that same kind of physical chemical information for estimating the amount that might be lost to the handwash recovery through absorption is lost information and it's a lost opportunity.

MR. DAWSON: I thing we're open to all possibilities and suggestions that you may have for how to address these issues.

DR. HEERINGA: I'm quite sure we'll have ample discussion of this topic later on.

Okay, at this point I think it seems like we're reasonably comfortable, at least with the presentations and the information provided this morning. There may be additional questions and I guess it's always been our practice, and I think Ken will follow that this afternoon, that if there is in the course of the discussion need for clarification or what appears to be a clear misunderstanding we'll allow an opportunity for a correction or a clarification at hat point too.

At this point then I would like to thank the presenters from the Health Effects Division for their discussion of the hand exposure measurements and that data. And I'd like to move on the next scheduled presentation on the agenda which is going to be presented by the Agricultural Handlers Exposure Task Force and the topic is a comparison of passive dosimetry in biological monitoring.

So we sort of go back to an industry evaluation of the topic that Doctor Beauvais covered this morning. And I think the scheduled initial discussion is Doctor John Ross if that's correct. Doctor Ross.

DR. ROSS: That's correct. Thank you, Mr. Chairman. I thank you for this opportunity to address this august body on behalf of the Agricultural Handlers Exposure Task Force. Can you hear me okay?

DR. HEERINGA: That's fine.

DR. ROSS: Today I'd like to talk about a comparison of human dosimetry as measured using passive dosimeters and biomonitoring. Next slide please.

I'd like to give a brief overview of what we're going to discuss today, starting with a history of worker exposure monitoring going back into time and then moving forward into the generic use of that

exposure in the form of the Pesticide Handlers Exposure Database, some of the attributes of passive dosimetry and biomonitoring and a review of studies that have been published as well as proprietary studies and some of the physical chemical properties, metabolism and things like that that are involved in comparing these different studies. Finally a statistical analysis, conclusions and some of the lessons that we've learned from these comparisons.

Passive dosimetry and biomonitoring go back to the mid-50s and correspond to the time of the introduction of the organophosphate insecticides where there was concern about acute toxicity.

These earliest measures of passive dosimetry and biomonitoring were industrial hygiene tools, they were done more qualitatively than quantitatively and that changed, the paradigm that we assessed risk with changed in 1983 with the issue of the National Academy of Science Report that established quantitative measures for exposure assessment. And we have gone from a time when we were trying to prevent acute toxicity now to preventing the possibility of no toxicity. We've gone from cases of toxicity in the field to a hundredfold below that with uncertainty for intra and interspecies factors, and are now entering a

new era where we're talking about looking at the 95th percentile at a hundredfold below the no affect level. Next slide.

Recently questions have been raised regarding the validity or the trueness of passive dosimetry as a measure of exposure. And I'd like to give an introduction to the generic use of passive dosimetry and a discussion of the criteria that we have used for biomonitoring, and then a comparison of the results of these two methods. Next.

The passive dosimetry methodologies have been codified, they were standardized starting here in 1975 with patch dosimetry by the World Health Organization. It was updated in 1982 for whole body dosimetry and there have been a series of FIFRA guidelines established for passive dosimetry. In 1986 for handler or mixer/loader/applicator exposure monitoring. In 1997 those guidelines were updated for reentry workers and residential exposure and in '97 the OECD issued guidance documents for passive dosimetry. Next.

The Pesticide Handlers Exposure Database has been discussed extensively today. So I'll try to minimize the reiteration here. But basically it was issued in 1992, reissued again with additional studies in '95 and these studies tended to be older, most of

them were non-GLP and as EPA has previously indicated there are 37 distinct exposure scenarios that are within the Pesticide Handlers Exposure Database.

The primary methods used for assessing dermal exposure was patch dosimetry and inhalation monitoring was typically done with personal inhalation monitors. Face and neck exposures were typically done with patch dosimetry in these studies and hand exposure as EPA has just discussed ran the gamut, there were a variety of methods. Hand washes with a variety of solvents, gloves, et cetera.

Now, one of the interesting things about the Pesticide Handlers Exposure Database is that two thirds of the dermal measures of exposure in that database are below the limit of quantification. The LOQ varied by a hundred thousand fold between these studies and reflected in part the age of the studies and the ability to detect different materials at the time the studies were conducted. Most of the studies didn't measure all body regions and as a result we, in trying to assess exposure, have added body parts from different individuals in order to come up with a whole body which we call composite bodies.

There are other synonyms for this. But the bottom line is that it's very difficult to get a useful

measure of variability from this type of data. So for the most part the Pesticide Handlers Exposure Database restricts the analysis to evaluation of central tendencies.

More recently the AG. Handlers Exposure Task Force has generated generic exposure data that follows many of the methods that have been established in the Pesticide Handlers Exposure Database, but improves on that paradigm. Next.

Now, basically for estimating total exposure in these passive studies, use the micrograms of exposure measured on a whole body inner dosimeter and the micrograms from the handwash, the amount of material from the head and neck and inhalation. Next.

Now absorbed dosage is calculated by adding in a compound specific dermal absorption fraction. So the data, whether it comes from the Pesticide Handlers Exposure Database or whether it comes from the AG. Handlers Exposure Database, is normalized dermal or inhalation to micrograms of exposure per pound of active ingredient applied. Multiply that by the pounds of active ingredient used in a particular study by the fraction of absorption through the skin, add to that the inhalation dosage which is also derived from a normalized value to pounds applied, and divide by body

weight to get absorbed dose.

Now, this is the critical comparison, this is what we use for comparison to biomonitoring which is also an absorbed dose. There are a number of exemplary passive dosimetry biomonitoring exposure studies that I'd like to overview today and show you the results from. These are a list of the studies in this slide. They include a variety of handler exposure monitoring studies, but they also include some reentry studies such as low crops, scouting, citrus pruning, citrus harvesting and an indoor study which is, actually two indoor studies which involved jazzercise. Next.

Now the requirements for a useful passive dosimetry study are ones that are able to measure both inhalation in the breathing zone of the individual that's being monitored as well as the dermal component which includes both a dermal dosimeter as well as hand washes and a measure of head exposure, head, neck and face exposure which can be done with either a patch or with washes and wipes.

We need to have an analytical standard and a good analytical method that allows low limits of detection. And it's important to emphasize that in these studies, especially where we're looking at concurrent passive dosimetry and biomonitoring, where

they are done at the same time, that there no additional layers of clothing beyond that required by the Worker Protection Standard or the label. Next.

Now for biomonitoring studies there are a number of desirable attributes and the ones that we've listed here we say are desirable, they're not absolutes but if we get outside of these parameters it becomes problematic. One thing that is required is a knowledge of the kinetics of excretion. We need to know what the metabolism and excretion is in humans or some higher primate. I can't tell you the number of times I have made the mistake of using rodent metabolites and trying to assess exposure. And this is a real problem when going to a higher mammal because sometimes the pathways for metabolism are radically different. It's helpful to have a urinary metabolite that's at least 30% of the absorbed dose. And we're going to discuss a few examples where we've got 8% to 12%. Those are still doable.

There are some examples that we have excluded that are as low as a tenth of a percent and we feel that those are not possible to make a reasonable comparison. Metabolite excretion has to take place over a relatively short interval, a half life of two days or less in order to capture a significant

proportion of the total excretion in a reasonable period of time. Especially if you're looking at 24 hour collections.

This is an imposition on people that are doing these studies or involved in the studies, involved in the collection and you don't want to impose any longer than necessary. Now metabolites need to be stable in urine and we need to know how the exposure occurs. That is, were these exposures study state? In other words, we know the person was exposed before we began monitoring and they continued to be exposed through the monitoring period, or was their exposure limited to just the time that we started the collection?

Again for these biomonitoring studies it's very helpful to have no additional layers of clothing beyond what is normal. And what I'm going to describe are studies in which individuals have been monitored in these concurrent passive dosimetry and biomonitoring situations where they have their normal work clothing which is long sleeved shirt, long pants and briefs and a t-shirt as the inner dosimeter.

Alternatively we can take an outer dosimeter and apply a clothing protection factor or penetration factor to that to estimate the amount going through the

clothing. But either way we're using normal clothing, nothing beyond that with these passive dosimetry biomonitoring studies concurrently done. Next slide.

Now in addition to concurrent studies there are a couple that we're going to talk about today that were consecutively done where we had passive dosimetry done in the same cohort of individuals that subsequently had biomonitoring done. It's desirable from our perspective to do this concurrently because under concurrent conditions you know that these people are being exposed to the same dosing scenario, whether it's handling a chemical or post-application exposure. And we're capturing that exposure by the passive dosimetry and biomonitoring at the same time. Alternatively you can use individuals, the same individuals where you've measure them at one time with a passive dosimeter and you might want to do this, and there are a couple of cases we'll talk about, where we're interested in extrapolating this data to residential exposure.

And so we put two layers of dosimetry garments on the individuals in the consecutive case so that we can find out what went to all portions of the body and then subsequently did biomonitoring using normal clothing configuration. There's a little

greater uncertainty associated with passive dosimetry and biomonitoring that's done consecutively than done concurrently just because you can't assure that it was exactly the same exposure scenario. It might be very similar in handling the same amount of material and in trying to engage in the same activities, but it won't be exactly the same. Next.

Now the concurrent passive dosimetry and biomonitoring study designs involved primarily garment dosimeters. There is one case where we used a study that had patch dosimetry, I'll point that out. Most of these studies were done more recently, that is 1990 vintage, plus. Virtually all of these studies that we're going to discuss that were passive dosimetry and biomonitoring concurrent, were done under good laboratory practices. Inhalation was monitored in the breathing zone for most of these studies, there are a few exceptions where exposure from the inhalation route was expected to be very low or nonexistent, and it wasn't taken. In virtually all cases face and neck wipes were used or occasionally hat patches. Hand washes were used in most cases. And in virtually all of these studies there was a high level of detectability, both in the urine as well as the passive dosimeters. Next.

Now of the 34 studies that we looked at, and these were both proprietary as well as published studies, 14 of the studies we found to meet the acceptability criteria that I outlined in the previous couple of slides. 9 of those were proprietary studies, 5 were published studies and 13 out of 14 of these "acceptable" studies used dosimetry garments. One of them was a patch dosimeter study. And 12 out of 14 were concurrent as opposed to consecutively monitored. Now, I'd also like to point out that in looking at these 34 studies there were other studies that were not included. One of those was the Propinyl study that EPA mentioned. In that particular study the metabolism was done in rodents and we felt that it was not a useful study for comparison to passive dosimetry. Next.

This slide outlines studies in the concurrent passive dosimetry and biomonitoring studies, the nature of the pesticide that was used in the left hand column, and then the next column over shows the human dermal absorption that was measured at the lowest dose in the studies where multiple dosages were measured. And as a comparison, the next column shows the rat dermal absorption for those same compounds and you'll not that as is typical, rats, when used as a model overestimate dermal absorption for humans, they tend to have more

permeable skin. In most cases the rat is the model of choice, that's what's used to generate regulatory data and so that represents one of the sources of conservatism when we estimate absorbed dosage from the existing data. We also show here the metabolite that was specifically collected in each one of these monitoring studies and in the far right hand column give an indication of the excretion after multiple half lives. Next.

Now, what we would like to discuss today is the validity of passive dosimetry as a measure of exposure. And Webster defines valid as having legal force, which is certainly useful in a regulatory setting or based on evidence or sound reasoning. A valid study or a valid methodology should give something that's reliable, that approaches reality, that's not overly conservative.

Now it's the AG. Handlers Task Force position that it's difficult if not impossible to isolate a particular portion of the body and validate exposure recovery to that portion. And that would be areas such as the hands, face or neck. The removal efficiency studies that are frequently done, some of those that have been recently cited in the literature, have problems with study designs.

They have short periods of application typically followed by wash off, they don't simulate what occurs in a working environment, they don't have some mitigating factors that would either prevent absorption, like the plant materials, grease, the equilibrium situation that occurs over an extended period when you're exposed to a recurring source. But all of these methodologies, the hand washes, the face wipes, the whole body dosimetry can be validated as a whole if we look at a comparison of concurrent passive dosimetry and biomonitoring. Next.

That is, if we look at biomonitoring and we find a dosage for a particular compound or a particular scenario, we compare that to the passive dosimetry dose estimated under that same set of conditions, applying a compound specific dermal absorption factor and they come out about the same, then we have a valid methodology. Next.

Now the method that was used for calculating dose for biomonitoring involved summing the amount of metabolite that was excreted and correcting for the stoichiometric difference between the molecular weight of the parent versus the metabolite, and correcting for the fraction excreted over the period of time for which the urine was collected and dividing by the body

weight. Next.

Now from the perspective of validating passive dosimetry with the concurrent biological monitoring we're going to look at ratios of central tendencies from each of these methodologies. We're also going to look at the possible influence of dermal absorption on this ratio of passive dosimetry to biological monitoring. And finally to look at the ratio over a number of different compounds and scenarios. Next.

Now the data that's shown in this graph are data from the Pesticide Handlers Exposure Database which is shown on the x axis and some data from the Outdoor Residential Exposure Task Force. These are central tendency values and they are compared to data from biological monitoring studies where the same amount of material was handled in both studies.

So the individuals, even though they came from different studies, the results were normalized to the same amount of material handled. And you can see the centerline, the solid line, which represents a 1 to 1 correspondence of passive dosimetry to biomonitoring. The dotted lines represent a plus or minus 3x difference from that centerline of equivalence. Next.

Now in manipulating the data, standardizing

the data for biomonitoring studies, or passive dosimetry monitoring studies that were compared to biomonitoring, we made some modifications from the assumptions that were in the original papers that were either proprietary or published. And these are critical because some of them involved for example, respiration rate where we adjusted all of the respiration rates to a uniform value of 16.7 liters per minute. In the studies as they appeared, published or proprietary, they were 12 to 29 liters per minute. I'll just point out that at 29 liters per minute, someone sitting on a tractor would hyperventilate and would be incapable of performing their job. But this was a regulatory assumption that was in common use for a number of years.

Biomonitoring data were consistently estimated using a combination of stoichiometry as I indicated and a percent excreted in urine after multiple half lives. Dermal absorption was adjusted in the case of Chlorpyrifos to a single value of 3%, because in the studies as published or as printed they ranged for that particular compound from a low of 1% to a high of 9.6%, reflecting the opinions of the various authors. 3% is the value that's historically been used for regulatory purposes, that's the value that we used

for all of the studies involving Chlorpyrifos.

In two fo the studies where we had concurrent biomonitoring and passive dosimetry, where only an outer dosimeter was used and they wore underwear but we did not measure the exposure on that underwear, we only looked at the exposure on the outer dosimeter, a 10% clothing penetration value was assumed. This is very consistent with data that has been accumulated by the Antimicrobial Exposure Task Force which shows a range of 8% to 12%. So we took about the middle of that range. Next.

This graph shows the individual data points for concurrent passive dosimetry and biomonitoring where the exposure from biomonitoring is shown on the x axis from passive dosimetry on the y axis and each one of these points represents an individual. So this is all of the data from all of these studies combined and you'll see that they fall above and below this line of equivalence that's been drawn in where there would be, if it fell exactly on the line, the same dose derived from both methodologies. You can see that there's perhaps a slight bias to overestimate from passive dosimetry, but it falls on both sides of the line. Next.

If we look at the ratio of passive dosimetry

to biomonitoring for these studies, again by individual, as a function of the dermal absorption factor used for the different compounds that were involved in these studies, we can see again that there's data that falls above and below this line of equivalence, the geometric mean ratio for all of these data points is 1.2 so there's a slight tendency to overestimate from passive dosimetry. Next.

Listed in this slide are, again the ratio of passive dosimetry to biomonitoring and we've just shown chronologically, the studies and the individual data points from each one of those studies to demonstrate that there is no particular bias in the results for passive dosimetry to biomonitoring as a function of time or study. Next.

In conclusion we feel that the data demonstrate that passive dosimetry does not underestimate the actual absorption or exposure as demonstrated or as measured from biomonitoring. It's not biased and yields an estimate of absorbed does that's very similar to biomonitoring. As a result of that we feel that passive dosimetry as a whole has been validated. And again we reiterate that it would be very difficult, if not impossible, to validate these individual measures that are used in passive dosimetry,

such as handwash, face wipe, et cetera. Next.

And finally the lessons learned here, regardless of whether we're talking about passive dosimetry using patches, that is from the Pesticide Handlers Exposure Database or from one of the studies that we utilized in the concurrent passive dosimetry and biomonitoring, or using whole body dosimeters, the absorbed dose from biomonitoring and the absorbed dose from these passive dosimetry are very similar. Biomonitoring however can only be done with a very limited number of compounds because we only have a limited number for which we have complete absorption distribution, metabolism and excretion data.

Finally, the dermal route is the predominant route across a variety of compounds, a variety of scenarios. Approximately 70% of the absorbed dose is attributable to the dermal route of exposure for these relatively low vapor pressure compounds. Thank you.

DR. HEERINGA: Thank you very much Doctor Ross. And before we move on with the additional segments of the presentation I'd like to offer the opportunity for the panel members to ask a few questions. Doctor Handwerger.

DR. HANDWERGER: In your discussion you presented all people as equal, but I'm not convinced

that the biometabolism of a 60 year old African American male is the same as a 22 year old Hispanic American female. I'm also not convinced that a 25 year old male on anticonvulsions or antidepressants or any drug necessarily metabolizes a particular substance the same as someone who is not on the same drug. I think there are a lot of internal cellular variables that have not been taken into account. Though your distributions, your correlations are excellent when you look at hundreds of individuals there is a lot of scattering of the results. And do we know more about the people who don't correlate as well as those that do? I would hope that the database would include things such as sex, something about the medical history, the age and so forth, because I think in your analysis all people were treated as equal and all people are not equal.

DR. ROSS: That's a very good point. You know, in response to that I think it's, would be useful to point out that a high proportion of the individuals involved in these studies were males, and that typically for whatever reason in the absorption, distribution, metabolism and excretion that are done by industry anyway, most of the participants are also males of about the same age range as the workers.

They are also typically screened to not be metabolically induced so that we're not looking at people that are in any kind of heavy drug regimen, non-alcoholics, et cetera.

So some of that variability that you're concerned about I think is not there. But the sex and the age and to a degree the ethnicity of these individuals is known, it's recorded, I don't think that it's ever been looked at, you know, in any kind of systematic fashion.

DR. HEERINGA: Doctor Barr and Doctor Chambers.

DR. BARR: Thank you for that nice presentation. I actually want to reiterate what he says. I think in the real world you're going to find a lot more variability. These are controlled populations with, you know, a fairly small range of age and a small range of ethnicities and so I think that you're going to find a lot more variability in the real world.

I have a couple of questions regarding some of your slides. Most of the slides didn't have what chemical you were talking about on them. When you looked at the biomonitoring dose versus the passive dosimeter estimate, were those all TCPY or TCP Chlorpyrifos or were they a combination of those

chemicals that you had on one of the first slides in your presentation?

DR. ROSS: Those were a combination of all of the chemicals.

DR. BARR: So you applied the same correction factors to each chemical? Assuming, you know, assuming 10% breakthrough and all of this stuff to each chemical, for each different chemical?

DR. ROSS: In the case where we had a consecutive, or concurrent with the outer dosimeter

DR. BARR: Uh-huh.

DR. ROSS: there were two cases like that, we used 10%.

DR. BARR: Okay.

DR. ROSS: Regardless of the chemical.

DR. BARR: Okay.

DR. ROSS: But in each case we adjusted absorbed dose by the chemical

DR. BARR: And by the pharmacokinetics of that chemical?

DR. ROSS: Right, by the kinetics of that particular compound.

DR. BARR: Okay. A couple of other questions. For Atrazine you measured the chlorotriazines. I'm assuming then you measured just

the Atrazine and the doculation products and no other chemicals there when you used those estimates?

DR. ROSS: No, I believe there were three.

DR. BARR: Three, so three.

DR. ROSS: I think Mercapturate was one of them.

DR. BARR: Well there's a great deal of variability with Atrazine metabolism, depending upon the exposure scenario especially and I find it hard to believe that biomonitoring and passive dosimetry compared that well.

The other question I had is you had on one slide Cypermethrin for Cyfluthrin and then the metabolite was the 440 3pba and so were you using Cypermethrin pharmacokinetics? Yeah, pharmocokinetics to estimate Cyfluthrin exposure, is that

DR. ROSS: No, the other way, well, yes. We were using Cypermethrin pharmacokinetics

DR. BARR: Okay.

DR. ROSS: for Cyfluthrin, that's correct.

DR. BARR: Well I was just, I was amazed at the way you data greed because before I came to this meeting I have never seen biomonitoring data and passive dosimetry data agree so well. Those are my

comments.

DR. HEERINGA: Doctor Chambers, I believe you were

DR. CHAMBERS: Just to clarify, the fraction excreted data, that came from human ADME studies?

DR. ROSS: Yes.

DR. HEERINGA: Doctor Ross, I guess Doctor MacDonald has a question.

DR. MACDONALD: Yeah, the graph on slide 22, is that in the advance material we were sent or is that something additional?

DR. ROSS: Oh, that is from another report. You were provided the report, let's see, the report is entitled, it's entitled, Passive Dosimetry Data Derived from Outdoor Residential Exposure Task Force and Pesticide Handler Exposure Databases, Comparisons to Biomonitoring Data. So it's an independent report.

DR. MACDONALD: Okay, and is, I think the, the two graphs showing the very strong correlation along the diagonal are very convincing arguments but like some other people here I'm a bit surprised at how good the agreement is, so I'd really like to see more documentation, in particular the, for example slide 22,

what was the sample size in each mean zone? Because that's also going to pull it into a more consistent pattern. So I would certainly like more documentation on those two pictures.

DR. HEERINGA: Doctor Ross, Steve Heeringa here, I'll just ask a question which I think probably needs to be asked in general scientifically. You went through a protocol, a process to review 34 studies and to choose 14 which show up in this graph and 20 were eliminated. Clearly in that review people knew or had information on what these relative dosimetry and biomonitoring values were.

How did you handle that in your review? I know I'm putting you on the spot but I think it's probably something 20 studies were eliminated from this graph

DR. ROSS: Uh-huh.

DR. HEERINGA: and in terms of criteria and scientific objectivity, how did the task force approach that?

DR. ROSS: That's a very fair question. Actually the summary of those studies that were eliminated for a variety of reasons is in Table 7 or the complete writeup.

DR. HEERINGA: Yes, uh-huh.

DR. ROSS: And, you know, the reason for exclusion is given in the far right hand column. And it varies. There were a number of studies that were excluded because there wasn't primate metabolism available.

DR. HEERINGA: Right.

DR. ROSS: You know, one of the studies that I did is included in that compilation. As I indicated previously I've been burned by assuming that primate and rodent metabolism are the same and only to find out later to my embarrassment that they are very different.

DR. HEERINGA: Okay, thank you for reminding me of that table. I actually did see that and I had forgotten I'd looked at that. So that, again I think it's just important to get that out here, to establish again the nature of those criteria for exclusion. Doctor Portier.

DR. PORTIER: If you could put up slide 26. One of the parameters that could actually make this better, and the one that I have the least understanding of where it comes from is the fraction absorbed.

You know, if I went through there's like three or four of these studies that seem to be way off

the mark and I, you know, like the Humnicutt study and you ask, did they just get the fraction absorbed wrong? If I tweaked it up so all of those points would move right up the one or the other one? The other parameters in this comparison seem to have pretty firm foundations.

Can you explain a little bit more where the fraction observed numbers come from? The 10%, I mean, you know, maybe 10%'s not right for that chemical under those situations --

DR. ROSS: Well

DR. PORTIER: or is that, I'm missing something here?

DR. ROSS: I think there's some confusion here because the 10% was clothing penetration but we applied a dermal absorption fraction, that amount getting to the skin of anywhere from I think 1% to, I don't know what the high was

DR. PORTIER: 9%, 1% to 9%?

DR. ROSS: Right, we've got it in one of the earlier tables. And that was applied on a compound specific basis.

Now, in many of those cases there were multiple doses tested in the individuals where the dermal absorption was tested and we typically took the

highest dermal absorption value of two or three values that were tested.

And typically the testing is done to simulate a range of exposures that might occur in a working environment, all the way from, you know, a reentry situation to somebody handling a concentrate. And so the values that we used tended to bias the, if anything, bias the estimates of passive dosimetry a little high.

DR. PORTIER: I guess I need a little bit more. How did they actually determine that number? I'm not a toxicologist so maybe at lunch

DR. ROSS: Oh that, I'm sorry

DR. PORTIER: you know, what I'm saying because that seems like a hard thing to get there. I mean I could see from the biomonitoring you could kind of back calculate what, you know, and under a lot of controls, you could back calculate what was dermally absorbed but how do they get that number otherwise?

DR. ROSS: This number is taken directly from typically human purposeful application studies in which a known area is delineated, typically on the volar surface of the forearm and material applied in a known concentration, it's normally radial labeled, there are a few exceptions. Actually Chloropyrifos was

one of the exceptions. But in most cases it's radial labeled so that they can follow the dosage and, you know, account for everything that was applied, removed and excreted.

DR. HEERINGA: Cynthia Hines.

DR. HINES: I'm sorry to beat a dead horse here but I just want to be absolutely clear on how this passive dosimetry was conducted concurrently. So we have an inner dosimeter process and an outer dosimeter process. And would you state again for the inner process what the worker was actually wearing and what items were then analyzed for the dermal exposure for both the inner and outer process?

DR. ROSS: Okay, that's a very good question. For the workers concurrently monitored with an inner dosimeter, the dosimeter that was analyzed for the skin surrogate was the t-shirt and briefs, okay? In addition to that I also looked at the area from the sleeve down, so the upper arm and forearm, to which a clothing penetration factor was applied to get to the skin.

DR. HINES: Because they had long sleeved shirts on?

DR. ROSS: They had long sleeve shirts with a t-shirt underneath.

DR. HINES: Right.
DR. ROSS: So in those cases there was
DR. HINES: Is that how the legs were handled as well?
DR. ROSS: Correct, yes.
DR. HINES: Okay, now the outer, could you go through that?
DR. ROSS: For the outer dosimeter studies the entire outer dosimeter was analyzed and an assumed clothing penetration of 10% was applied to everything that was on the outer dosimeter.
DR. HINES: And they had their regular work clothes underneath?
DR. ROSS: Correct. Well, underwear, yes.
DR. HINES: Just underwear, no
DR. ROSS: Just underwear.
DR. HINES: Okay, so it was a dosimeter and underwear
DR. ROSS: Correct.
DR. HINES: no t-shirt. Okay. A full body dosimeter, their underwear and no t-shirt?
DR. ROSS: And no t-shirt.
DR. HINES: Right.
DR. ROSS: Right.
DR. HEERINGA: Doctor Lu.

DR. LU: Yes. I heard it said by Doctor Heeringa yesterday that all the discussions outside this room should be disclosed. And some of the panel members actually gathered together at the dinner table last night to continue the discussion and one of the topics was that we wonder how a so called generic database can be established for the purpose of these topics. By listening to your presentation, again this is my understanding, I just want to double, I don't want, I just want to make sure that that's correct, by comparing the passive dosimetry data to the biomonitoring data, regardless of how you do it, you find a very good consistent, you find a very good correlations, therefore the conclusion made by the task force is that we don't have to worry about individual locations of the passive dosimetry data as long as we use the whole body dosimetry, that number alone will be sufficient to say use for those calculations. Is that somewhat

DR. ROSS: That's

DR. LU: close enough?

DR. ROSS: That's correct.

DR. LU: Okay. The question is, yesterday somebody from your group presented the whole body dosimetry figures that kind of, you have 6 regions,

right? Like arms, back and my question to the Agency actually earlier prior to the presentation was, how are you going to process the samples? Say at the end of the study period the person has the whole body dosimetry and obviously the person has to take the dosimetry off, are you going to cut the 6 regions and analyze individually and add it together? Or

DR. ROSS: That's correct.

DR. LU: Okay, so the question is, it's a big surface area, it's made of cotton so it takes up a lot of solvent to extract a compound.

DR. ROSS: That's right.

DR. LU: Don't you worry about a limit of detection?

DR. ROSS: That's part of the methods development in choosing your surrogate compound. You have to be very careful in going into one of these studies that you can get down to the limit of detection that you need, knowing that when you extract these large surface areas and you're generating large volumes of solvent, that you can get down to these low levels of detection. I mean we're looking at nanogram per centimeter squared, or less, detection limits.

DR. LU: Well I think, well, we can talk about this later this afternoon during, in our

discussions.

DR. HEERINGA: We will have opportunity. Thank you, Doctor Lu. At this point I think what I'd like to do is to move on to make sure that we get in the balance of the components for the presentation.

And I think that Curt Lunchick is going to do the next segment of this presentation and then Doctor Baugher after that I believe.

MR. LUNCHICK: That's correct and I want to again thank the panel for the opportunity to present the Task Force position. I think the discussions that we've had so far this morning have been very enlightening and very good.

What I want to do is kind of move what we've been hearing into a regulatory risk assessment and how this type of information gets used and the Task Force's position on what we're hearing in regards to how our data would be used by the different agencies in North America to conduct a risk assessment and what we think the proper conclusions are. Go to the next slide.

The charge questions that we're looking at right now, in addition to whether there is a need for additional data, basically boil down to whether we should be adjusting any part, individual part of the passive dosimetry methodology, the hand monitoring, the

whole body dosimetry as your breakthrough.

We've looked at different studies, we've clearly looked at this comparison of passive dosimetry to biological monitoring to determine if the methodology as a whole is consistent and is not systematically underestimating what we consider to be the true absorbed dose measured through biological monitoring. And obviously one of the options that the Agency has presented is to make no adjustment based on this correlation that we are seeing. Next slide.

John raised this issue and I wanted to emphasize it because I think we need to make a very clear distinction between the issue of efficiency versus validation. We've seen data presented by the Agency, looking at the removal efficiency of pesticides from the hands with different techniques, be it rinse aids or touching tubes, et cetera.

That clearly gets in to whether the percentage of material you're removing is high, low or in between. What it does not get at is whether any one method is more or less accurate in regards to the prediction of the true absorbed dose. And I think as the panel deliberates the charges questions it needs to keep this in mind and differentiate between efficiency and validation. You can go to the next slide.

Clearly I think we saw, I think the Agency did a good job in its presentation that there's a lot of stuff going on when we're looking at what's going on in the field in hand rinses, glove dosimeters, whatever and if you look at the data as a whole it was hard to tell if there was any real consistent difference. There's a tendency to think that cotton glove dosimeters give you slightly higher residues than a hand rinse which give a slightly higher residue than the hand wipe, but even that is questionable as to whether there's a difference of if it's consistent. And the Task Force, we have standardized our hand monitoring methodology with a hand wash which adds a physical removal process compared to a rinse where you may just pour water or whatever monitoring material over the hands.

That said, I think again one has to keep in mind, I know everybody including the Task Force wants to ensure that whatever our methods are, we are not underestimating the calculated absorbed dose and henceforth, risk. But we also have to be careful, and as Doctor Baugher is going to present, higher estimates through some of these methods may not actually be the best. Higher dermal residues may not be more accurate, they're definitely going to be higher and obviously

overestimate compared to others, but as Doctor Ross was showing, in validation you want some level of accuracy there.

And I think this is consistent with what the Agency has concluded too on page 82 of its submission, that if you look at these hand rinse efficiency studies, the results are equivocal in determining if one is better than the other, it consistently gives higher residues. And frankly that was consistent with our selection criteria we discussed yesterday where we did not make a preference in reviewing existing study data. Next slide.

Our position therefore is, and again this is the other important point, you have to look after what we are doing in estimating the total exposure in absorbed dose, that you've got to look at the methodologies combined, the whole body dosimetry, the face and neck wipes and the hand washes. Our methods follow, do follow the EPA Guidelines, we are providing consistency in our new studies that we're conducting with doing the handwash methodology.

And that, if you look at these comparisons of dermal exposure or the absorbed dose calculated from the combined dosimetry, hand washes and, or hand exposures and face and neck wipes, adjusting for human

dermal absorption, and it's important to note, remember that in these ratios you're seeing it is human dermal absorption we are using, that we are getting very good correlation with the absorbed dose calculated by the biological monitoring.

We found it interesting that the analysis we did was coming up with a ratio very similar to the one that the regulatory agencies did, although they were done independently. Which again raises the question, if the methodology as a whole is considered accurate for the purpose of calculating the total absorbed does, then why do an adjustment for hand exposure even if it's a small adjustment? The question needs to be considered, is it necessary?

That said, we think there may be situations where determining the hand rinse efficiency is important. They're not the situations the Task Force is going to primarily look at, but if one of the members is looking at hand exposure by itself for comparison of say exposure mitigation with different types of gloves or in other ways comparing just hand exposure, this issue of making sure those exposure values by themselves where you've got high efficiency of removal, that the values you['re getting are reflective of what's on the skin, then we see

situations where looking at the hand rinse efficiency may be important.

But for what we're doing, again with total dermal exposure estimates we feel the methodology has been validated to a degree that we have confidence in its ability to predict the absorbed dose when adjusted with dermal, human dermal absorption.

The other issue that was raised is maybe to look at a well established chemical where we know the human ADME values and to determine if any breakthrough of the whole body dosimeter is occurring. This is an interesting idea I think conceptually, it makes sense. The problem is, and we saw this this morning in Doctor Beauvais' presentation and I think in some of the discussions that are being raised here. There is a lot of complexity in what's actually going on out in these fields.

This is not a controlled circumstance by any means when we go out and do a field study. Individual variability in how products are metabolized, I mean there's differences in the exposure to different parts of the body which would affect dermal absorption. I question whether we have enough accuracy to take the absorbed dose in this type of situation, subtract out inhalation exposure, account for the hand exposure and

face exposure and accurately determine whether there's any significant breakthrough coming unless it's pretty significant.

And frankly, with it being under the normal work attire and with the levels of exposure we're seeing, saturation or those type of situations really aren't occurring. So again, I think we concur with the Agency that on the whole the potential breakthrough of a whole body dosimeter is probably very small, it may occur to some degree, but with the overall accuracy that we're looking at here it probably does not require looking at concurrent biomonitoring to see if we could adjust. You can go to the next slide.

And I think the Agency concluded it very well in its submission where it states that, you know, the dermal absorption during sample collection and breakthrough through dermal dosimeters does not, you know, it's unlikely to contribute to a negative bias in any pragmatic application of the results in a risk assessment. And I think that's the key is the word, pragmatic. You know, for regulatory purposes whatever is occurring is so negligible as to, it's questionable whether you could measure it accurately and its impact on the exposure assessment is going to be minimal or unlikely.

Again, and I'm just going to quickly go through this because these points have been raised now several times, but an adjustment of the passive dosimetry techniques as a whole, and we emphasize on the whole, is unnecessary because we are seeing this concurrence with the biological monitoring. And what makes it even more important is, as Doctor Ross said, typically when we're doing a risk assessment we will take the data, the passive dosimetry.

We will not have human dermal absorption data and with the new human subjects rule I can guarantee you that it's going to be very unlikely there's going to be some extremely strong need before any of our companies conducts a human dermal absorption study.

So we're either going to be using rat dermal absorption data determined by guideline methodologies which as you saw in one of Doctor Ross' slides tends to be much higher than the human dermal absorption, or frankly there are times in the absence of even rodent data with the EPA, a default of 100% is used. So you have these confounding conservatisms to the passive dosimetry as we get into estimating absorbed dose to calculate the risk values.

I think basically this is again reiterating that we've seen no evidence from what the Agency has

presented and our own analysis, that the AHETF passive dosimetry methodology, frankly the guideline methodology taken as a whole, is systematically underestimating the absorbed dose. And if this panel agrees with this analysis, and again taking into effect also the fact that typically we're not going to use human dermal absorption, we're going to be overestimating based on rodent or 100% dermal absorption default, that the passive dosimetry methodology is sufficiently robust and accurate, that a correction factor is not needed for regulatory risk assessment. And I believe that's my, yeah, last slide.

DR. HEERINGA: Okay, thank you very much. At this point what I'd like to do, I will leave time for questions but I'd like to go on to Doctor Baugher's presentation and then we can return for general questions for Mr. Lunchick and Doctor Baugher. I hope I've pronounced the name correctly, I think I said it, Bauer, earlier but it's a hard G.

DR. BAUGHER: Thank you and I'm glad to be allowed to speak in this issue. My name is Doug Baugher, I'm a technical consultant to Gowen Company and represent them on the various ag. and residential exposure task forces. I've been deeply involved in pesticide exposure assessment and risk assessment since

1980.

Let's cut to the chase and go to slide number 2. The issue underlying charge 2 is the adequacy of passive dermal dosimetry, specially, does it underestimate exposure? Or another way of putting it, are the methods sufficiently accurate for their intended purpose in risk assessment and risk management?

Give that concern, what can we do? We can validate methods, that's the dosimetry methods for the surrogates that we use. We could apply an arbitrary adjustment factor to the measured residues. We could biomonitor for residues not sampled. Or we could do nothing.

Except for the last action there are difficulties with the other three approaches. As other presenters have noted the dermal acquisition and retention of residues is a complex process that we really do not understand. And for that reason, here we are 30 years into it, we still do not have a validated protocol for even the simplest issue, residue recovery and efficiency.

And we have to note that truly validated methods would be much more than residue recovery efficiency, they would have to simulate the dynamic

processes occurring in the field. And we also note that developing such protocols would require intentional human dosing with a clear justification. We'll try to show you later that we do not believe there's a good argument for justification.

Biomonitoring to measure residues that escape capture by the dermal dosimetry could be useful but that would require human pharmacokinetics, discovery of good biomarkers and development of analytical methods for urinary metabolites and so forth. Because the current products for which we have such information are not our surrogates and are not suitable for surrogates, developing this data would be very expensive and probably not meet the test for justification.

Applying adjustment factors to the dosimetry methods has been suggested but as we have seen, the efficiency based factors would be all over the map and determining adjustment factors that satisfied the regulatory agencies, the scientific community, the public, the stakeholders would be very daunting.

In any case, the issue as it applies to exposure task force work is based on a simple model that we've seen before. Dermal exposure totaled equals the hand plus the body plus the face and neck and as we do it that's from hand washes, underwear and swabs.

The ultimate product of our model, if the ultimate product of our model was based only on these three parameters, then the measurement uncertainty would be a real concern. As an aside, the comparison of biomonitoring to passive dosimetry as presented earlier is a classic case of validation of the three parameter model. But the ultimate goal of our work is to produce an estimate of the absorbed dose for use in risk assessment and risk management and this is multi parameter.

This slide shows the usual parameters in that dermal exposure monitor, model. The column labeled, convention, shows the usual regulatory conventions and the column labeled, expected, shows parameter values likely to be found in the real world. Now this of course will vary product by product, though what I have shown here is typical of many orchard products. And I've selected open cab air blast application as the model here because it's a very high exposure scenario. In the regulatory convention the agencies would assume 100% of the maximum labeled rate per acre.

Typically it's about half that and it can go greater or lower depending upon pest infestations. The Agency estimates 40 acres per day. I've talked with many growers and pest control operators and they're

very happy if they get 30 per day. And oftentimes only a single block may be treated with a product so it could be only 5 or 6 acres per day. The dermal milligrams per pound AI handled, the unit exposure we've talked about would be the arithmetic mean under convention.

We would probably use the geometric mean because the distribution is lognormal. The body weight conventionally is 70 kilograms. Our workers happen to be just a little bit heavier than that. In the AG. Handlers Air Blast Study which I've used here, they averaged 89 kilograms and over all the studies that we've done they 've averaged 89 kilograms. So when we're done we calculate dermal mgs. per keg per day in the usual fashion. And we see that the conventional calculation gives us a value approximately 5 times that of the expected value.

Now the next component in the model is dermal absorption. And typically when we have a lack of rat dermal absorption data we use a conventional 100%. Now, this does not account for the other important component which is the differential between the rat to human which is probably on the order of 2x to 10x and has been historically reported out at 5x. If we do have a rat dermal absorption study we use that data,

but again we don't account for the rat to human differential. And finally we might have in vivo human dermal absorption.

I'm going to look at how this use of dermal absorption really affects what happens to the entire multi parameter model. I'm going to label these conditions 1, 2, and 3. Condition 1, we have human dermal absorption, that's seldom the case. Condition 2, we have rat dermal absorption, that is sometimes the case, and we can alternatively model the 5x rat to human difference. And finally condition 3, where we have no dermal absorption data the Agency assumes 100% rat dermal absorption. Here again we do have knowledge. California put together a review of I think 42 rat dermal absorption studies and found that the mean absorption was 19% plus or minus 14% and they used that knowledge to establish their default at 50%.

So anyhow, if we apply these conditions to the conventional deterministic estimate we see that in condition 1, with known human dermal absorption the conventional model estimates absorbed doses 5 times greater than the expected model. Under condition 2 with known rat dermal absorption the conventional model estimates absorbed doses 25 times greater than expected when the mean rat to human differential is factored in.

Under condition 3 with unknown rat dermal absorption the conventional model estimates absorbed doses 120 times greater than expected when the mean rat to human differential and the historical mean absorption are factored in.

In short, the conventional approach to getting an absorbed dose yields estimates substantially greater than would be expected when other knowledge is factored in.

You may be wondering if I'm mixing apples and oranges here and so forth but I took another step. To assure myself that I had not fooled myself with these central tendency and high end estimates, I did a couple of simple probabilistic analyses and we'll go over the results of that in reverse order.

What I did was, I'm not going to show you the whole model because it's very simple, I accounted for handwash residue collection efficiencies of 60% to 95% which is based some work that Doctor Ross has done with rats and the removal in rat dermal penetration studies. Whole body dosimetry efficiency, I let it range from 80% to 99%. Face wipe, 75% to 90%, 95%. In any case, when you look at all the input parameters, the bottom line is the driver was the unit exposure and the lognormally distributed milligrams per pound AI

handled.

Now where am I here, okay, so what we found is, factoring in the dosimetry and efficiencies had a very minimal impact at the high percentiles. For example, a 98th percentile dose, assuming 100% dosimetry efficiency might become a 96th percentile. So although these ranges of inefficiencies look pretty high, when you factor in everything you can that's going on they really don't have much of an impact. More importantly, no matter how you look at it the conventional estimate of absorbed dose always approached or exceeded the 95th percentile and many times it was at the 99th or higher.

Now, another important thing is, this is an exposure assessment based on acute exposure. This same value would be used for a long term exposure and when you compare that to the probabilistic overall mean it really vastly overestimates that exposure.

Okay. So to conclude, passive dermal dosimetry is only a component in the overall estimation of absorbed dose. When used with other model inputs conventional deterministic estimates give high percentiles even if you account for residue collection inefficiencies. And one again this is another confirmation of the phenomenon that we call compounding

conservatisms.

We admit that the current dermal dosimetry methods may have some minor limitations and we don't see that there is much benefit to be had by finding out what those limitations are. Therefore there is no meaningful benefit and therefore the intentional dosing for additional dosimetry method validation would not be justified. Applying the arbitrary adjustment factors would be inconsistent with the risk/benefit principle of FIFRA because there's no real benefit. So we take the recommendation of the fourth action which is no action. Thank you.

DR. HEERINGA: Thank you very much, Doctor Baugher. We are at 12:15 and I think in the interest we've made good progress here, I'd like to give the opportunity for panel members to ask a few questions before we break for the lunch. I think that as I mentioned this morning I need to go to College Park to teach this afternoon, but Doctor Portier will be assuming the role of the Chair and I think he'll leave an opportunity right at the start of the afternoon session for any questions that may arise over lunch.

Any questions at this point from the panel, questions of clarification? Ken.

DR. PORTIER: In your analysis you

adjusted for body weight by moving the kilogram body weight up from 70 to 89, right?

DR. BAUGHER: That's correct.

DR. PORTIER: I think that's on slide 7.

DR. BAUGHER: Yes.

DR. PORTIER: In estimating the dermal exposure did you change the biometrics to adjust for the higher weights? I mean, you know, body size, as you put on weight the skin surface area goes up as well so your exposure amounts subtract that a little bit as well. So did you back calculate that or did you use the standard biometrics?

DR. BAUGHER: I did not back calculate that but in other little numerical experiments I've done I've found that there's really not much correlation between body weight and between dermal exposure. Yes, intuitively bigger weight, bigger surface area but it just doesn't seem to work out that way.

DR. HEERINGA: Doctor Popendorf.

DR. POPENDORF: I've got, yeah, two questions that are just informational on John Ross on one. Your slide number 24 that showed those individual values comparing dosimetry and biomonitoring, did you happen to run a correlation coefficient for that slide?

DR. ROSS: Yes, and I believe that's in the writeup. It was, well, we didn't do a correlation coefficient per se but we did look for correlation.

DR. POPENDORF: Yeah.

DR. ROSS: And it is highly significant, I think less than 0005 and I believe that it's in the text of the article here.

DR. POPENDORF: Uh-huh, I, we, I can maybe look for that. The other question was a clarification I think on Curt information. A couple of you mentioned that when you were talking about that default absorption for, you know, when you don't have human data of 100%.

DR. ROSS: Uh-huh.

DR. POPENDORF: Now is that 100% of dose or 100% of the rat absorption fraction?

MR. LUNCHICK: Okay. Curt Lunchick. Typically what we do is, if there are no dermal absorption data whatsoever, rat or human, we will take the dermal exposure value and assume it's totally absorbed so it becomes equivalent to dose.

DR. HEERINGA: Doctor Landers, do you have a

DR. LANDERS: I have a question

DR. HEERINGA: Turn on your microphone

please.

DR. LANDERS: On Table 7 with the open cab air blast applicator, on that table I compliment you on choosing 30 acres a day as a more realistic output, I would agree. But I'm somewhat concerned about you taking 50% of the AI per acre. When were these trials conducted?

DR. BAUGHER: Could you go to my very last slide, I don't know if it's on there or not. In the probabilistic analysis I used as an example some various orchard products I've worked with and looked at the most likely use rate of being 50% of the maximum label oh, I'm sorry, I'm reading the wrong column here, if you go down to the pounds AI per acre

DR. LANDERS: Uh-huh.

DR. BAUGHER: you see that the product may be used at 1.5 to 3 pounds active per acre in that discreet distribution

DR. LANDERS: Yes.

DR. BAUGHER: and that 20% of the time it'll be the low rate and 50% of the time it'll be near the average and 20% of the time a little above and about 10% at the maximum. And that's based on experience with some of the products I've worked with.

DR. LANDERS: Right.

DR. BAUGHER: Now this would vary case by case.

DR. LANDERS: Yes, because it, for example in New York State until three years ago it was unlawful to go below the maximum rate. So, indeed, so this would not be acceptable to us on the east coast.

DR. BAUGHER: Unlawful to go below the maximum label rate?

DR. LANDERS: Yes. Correct.

DR. BAUGHER: I have never heard of that.

DR. LANDERS: And the reason for this is resistance.

DR. BAUGHER: Okay, then I guess I'll take New York out of my models.

DR. HEERINGA: Or put it in your fourth category. Yes, Doctor

DR. ROBSON: Hi, Mark Robson, just as an aside, under FIFRA, as somebody who been training pesticide applicators for years we always encourage below the rate, as does the Agency, and under FIFRA 2EE we, the farmer can legally do that. The registrant at times is anxious about efficacy and reminds of that, but at least in your neighbors in New Jersey we encourage below the label rate.

DR. HEERINGA: Doctor Hughes.

DR. HUGHES: Yeah, I'm, just a point of clarification, I'm assuming this is a sensitivity analysis as to which inputs would have greater impact in the probabilistic model. Have you ever done that for like residential or reentry models?

DR. BAUGHER: Yes, as a matter of fact I forgot to mention, I did a very similar analysis with reentry into treated orchards to hand harvest fruits, again factoring in residue collection inefficiencies and reached exactly the same conclusions. The drivers there happened to be a little different. One is the variance in the transfer coefficient and the other is the variance in the residue which depends upon the day of reentry. But again it's our unit exposure that the task forces have measured which is the most important component of the probabilistic models.

DR. HEERINGA: At this point I think I would like oh, Doctor Lunchick or Doctor Ross.

DR. ROSS: One response to Doctor Popendorf, the statistical correlation for that second figure with the scatter plot is located on page 33 of the report and we looked at the Spearman Rank correlation with a p less than 0001.

DR. POPENDORF: And that's, that I guess certainly is significant, I was just looking to see

what fraction of the overall variability was explained by the agreement or the difference, which is the square of the correlation coefficient so, but thank you.

DR. HEERINGA: Dallas.

DR. JOHNSON: Yes, significance in correlation is more a function of sample size in the actual value of the correlation. So could you tell us what the actual value of that correlation was for that picture?

DR. HEERINGA: It must be an r square for that regression line if it's a linear. I see .672.

DR. JOHNSON: I was going to say .7 just by looking at the picture so I was pretty close.

DR. HEERINGA: Okay, the interocular test here. At this point in time I think that I would like to call a break for lunch and again I think 1:30 Ken?

DR. PORTIER: Yeah.

DR. HEERINGA: Let's reconvene at 1:30 at which point Doctor Portier will be chairing. I want to make one comment before we break and that is, with regard to the proceedings I want to make sure that everybody is aware that there's a lot of material, we have broken up the presentations and the discussion of the charge questions, primarily so that I think all of us can stay a little more engaged. Because if we had

12 hours or presentations and then 12 hours of charge of charge question discussion it just would not be effective.

What is going to happen over the course of these four days is that we will discuss charge questions at the appropriate time frame following the scheduled presentations.

If there are additional thoughts or additional information comes forth as a result of future presentations or actually conversations such as we've had this morning, it will be possible to revisit for panel members a charge question I think. And we can do that at the beginning of each day just to make sure that as we proceed through Friday that if there are any changes or any additional information or comments pertaining to those charge questions, that that can be brought forward. I think that's only fair game in this process. And if not, we wouldn't sort of have a full exploration of the topic.

So hopefully everybody will be here for the four days, from the critical players to the public who has a vested interest, obviously from the task force and from the EPA staff. If for some reason key individuals will not be here over the course of the next two and a half days you may want to bring it just

to the attention of Myrta Christian and myself so we can accommodate that.

Okay everyone, have a good lunch and I think for panel members and others, I don't want to advertise a particular location but I think the Hyatt's expecting some people and has some tables reserved over there.

(WHEREUPON, the morning session was adjourned for lunch.)

FIFRA SCIENTIFIC ADVISORY PANEL (SAP)
Review of Worker Exposure Assessment Methods
January 10, 2007
Afternoon Session

DR. PORTIER: So let's reconvene. This morning we had a good set of presentations and some good discussions. At this point, before we go into the charge questions I'll give the committee one last opportunity to ask any clarifying questions of the presenters from this morning.

Do we have any open questions, burning questions that were developed over lunch?

Yes, Doctor Appleton.

DR. APPLETON: Just something I forgot to ask yesterday. When does the task force anticipate the availability of a beta version of the AHED for public examination?

DR. PORTIER: Identify yourself.

MR. LUNCHICK: Yeah, I will, this is Curt Lunchick, Task Force Bearer Crop Science. It is available already with data that have been reviewed and frankly I could get you a copy, Hank, and if anybody else on this panel would like to see the database, I think maybe work through Steve Knot or somebody to get a list and the Tash Force will distribute AHED. It's I

think build 3.6 for people that are curious.

DR. APPLETON: Can I, just one more quick one if I can remember it. Did you have any plans to, I hate to use the word validate, but like field validate the database once it's established in a form that everybody's comfortable with and come in with a study that's been designed according to your criteria and performed and just compare the outputs of the exposure between the two?

MR. LUNCHICK: Well the database, I'm not sure I got the question, the database is much like PHED, a compilation of existing study, or study data that it then does the algorithmic calculations. So I'm not quite sure what you were wanting us to validate it against. We are, just out of curiosity going to compare it to PHED estimates but

DR. APPLETON: Uh-huh.

MR. LUNCHICK: and it is there for somebody to, for instance, look at a scenario where you feel there is sufficient data and compare it to biological monitoring.

DR. APPLETON: Yeah, okay, just curious. Thank you.

DR. PORTIER: Okay, I guess we're done with the questions and it's time to move on to the

issues and the charge questions.

We're starting out here at around 1:40 and we're scheduled to go to 5:30, just to warn you, we're going to cover all three questions that are on there today so we may be running a little beyond the 5:30 period but not much more than that. It all depends on how the conversation goes.

So with that I guess, Jeff Dawson, you're going to be reading the charge questions.

MR. DAWSON: Okay. Question 1, data needs. EPA believes that many studies within our current database have limitations. In some cases the Agency is lacking data to address modern pesticide application equipment and techniques. EPA believes that additional data could significantly improve our ability to estimate and better characterize the range of worker exposure with greater certainty. Please comment on these limitations and EPA's conclusions that additional data could improve significantly the Agency's ability to assess worker exposure. Also, please comment on the selection criteria proposed by the AHETF and AEATF and their respective submissions for evaluating the extent to which existing data would meet EPA's exposure assessment needs. Thanks.

DR. PORTIER: And our lead discussion on

that is Doctor Curwin.

DR. CURWIN: Okay, thanks. I'd just like to start off by summarizing a bit of what I understand are the limitations of PHED and the reasons for this first charge question.

Essentially from what I've read and heard, the PHED essentially has an inadequate number of measurements or at least quality measurements. In some cases inadequate QA/QC, use of older sampling methodology, for example the patch dosimeters versus using the whole body dosimeters, older analytical methods that may result in higher levels of detection with the resulting in high levels of censored data. I think one estimate was that there was two-thirds of the data in PHED are actually censored.

Lack of representativeness and by that I mean the older work practices that may no longer be used are in PHED and some new technologies and new practices aren't reflected in that database. As well a lack of diversity of test conditions and a lack of entire body dermal estimates.

So the EPA contends that these limitations decrease the confidence in the reliability in some of their exposure estimates for pesticide handlers that there are making for regulatory decisions.

Given these limitations I think that there's an impetus then to try to develop this new database that will address these limitations, however there are some people that have questioned the need to replace PHED or don't think it should be entirely replaced. The Farm Worker Justice presented yesterday as well as a comment by Doctor Richard Fenske suggests that PHED has 1,700 plus monitoring units and that the new database will only have about 600 monitoring units, and that therefore we shouldn't be abandoning PHED just yet.

To that I actually, and maybe the Agency might be able to help me on that, I've had some experience with PHED in the past and, although there may be 1,700 plus monitoring units, the actual number of units that are used in regulatory risk assessments is much, much smaller if you limit it to the grade A and grade B data. And so that is my assumption. So in that regard I'm not sure if it, if the number of monitoring units, how that will compare to then the new database.

But given that there is some useful data I think still in the PHED, and one of the comments that I've heard is that even though the newer technologies are maybe not captured in PHED and that the new

database will capture these, we don't want to lose the old technologies that are still being used in some cases, you know, particularly with certain types of tractors and things that can be used for many, many, many years.

It's my opinion, and this is just my personal opinion and it certainly isn't that of the panel, and we'll have this discussion about this, but I think that the EPA has clearly demonstrated that there is a need for new additional data. I think the limitations in PHED, and I've had the experience of using PHED for risk assessments, I think these limitations are valid, that the ability to conduct a worker exposure assessment is limited because of these limitations. And certainly by requiring additional data that will address these limitations will help I think the Agency is improving their risk assessment and their exposure assessment process.

Given that though, the new database certainly has to be designed such that it addresses these limitations that have been noted. I would also encourage that PHED isn't completely abandoned and I think this is being done but that's certainly, some of the data from that database is going to be incorporated into the new database and existing studies that are out

there now are going to be incorporated into the new database.

To comment on the criteria that was used by the two task forces in selecting data to go into the database, my assumption is that this is selection criteria for existing data, the criteria seems reasonable to me. I do have a couple of comments, one for each of them actually.

The AHETF in their criteria state that inhalation data is not required and this meeting so far has largely been speaking about dermal exposures and I understand that dermal exposure is a significant portion of exposure when we're talking about pesticide handlers, although inhalation still can be a significant contribution to exposure and we haven't addressed that in this meeting at all. I would think that part of the criteria for including data you would want to still include studies of having inhalation exposure.

With regards to the AEATF they state in their criteria document that they'll use biomonitoring data to populate a database, a generic database, provided that there is acceptable primate dermal exposure and pharnacokinetic data. I actually question the use of using biological or biomonitoring data to populate a

generic exposure database. You're going to have to back calculate to get your unit exposures which is going to introduce some error and uncertainty and then you're going to take this value and then apply a dermal absorption dose or some other metrics to come up with an absorbed dose, so you're actually doubling the error in some regards. At least figuratively if not literally. So I would question that, although I think biomonitoring data is is very useful and should be considered in certain instances. But I think to populate a generic database for developing unit exposures, I would caution against that because of this error.

That's all I had to say directly on this and I'd like to just open it up to the assistant discussants and have their opinions as well. If Doctor Appleton would like to start I'll just go in order on this sheet.

DR. PORTIER: Remember to speak up now.

DR. APPLETON: Yes sir, yeah, it turned itself off. Hank Appleton, Forest Service.

Okay, I guess my first comment would be to recommend that the EPA and the task forces examine the available methodology that is out there in the literature involving the use of physical chemical

properties to estimate dermal permeability constants with the pesticides of interest to these databases. It would be a first step towards using first order kinetics to examine absorption, systemic absorption and determining the absorbed fraction of residue, perhaps in terms of percent of external dose absorbed per hour. I think that would be injecting a little realism into the scenarios that we assess.

The second comment I had, now I may be mistaken, but in listening, particularly to the AEATF discussions of yesterday and today, there seems to be a proposed approach that will minimize variation between monitoring units or replicates as we used to call them. And that really wouldn't promote probabilistic approaches that the EPA is promoting right now and it really seems to me to be a compromise of realism for what may appear to be a cleaner study statistical design and result. That's a personal opinion rather than an observation.

And final well, I've got two more. With to hand residue collection, in view of the existing data and just the priority knowledge, with the existing data showing possible rapid absorption of some active ingredients in pesticidal formulations, the use of hand rinses is questioned by me and I think a number of

other people, including Howard Mybach, as a data collection technique.

And certainly for future studies we ought to determine whether or not we want to continue with the use of the rinses, whether it's because of the detergents in the alcohol can change the physiological nature of the epidermis or deeper layers. And particularly I hadn't really thought about the calls of nature too much, I was too hung up on the physical properties of chemicals and how they dermally absorb, but if there are going to be repeated hand washes within a study monitoring period then that, the possible changes in the skin properties that I think tend, would tend to accelerate dermal absorption may occur.

On the other hand longer term residences on the hand surface raises the possibility of dermal metabolism of residues and that would be a residue that you could lose over a four hour monitoring period. And then of course the obvious systemic absorption that could occur within that four hours.

And because of all these confounding factors that can go into the hand rinse technique, you know, my personal recommendation would be at least to reconsider hand rinsing techniques for the newer studies or lose

them and go with a cotton glove external dosimeter instead. Maybe with frequent changes of gloves if you're worried about breakthrough. But you'd have to consider the level of detection that you're working with.

And everybody's going to talk about the statistical validity of 10 monitoring units per study but my personal opinion is I'd rather have 10 quality replicates to work with than 15 or 20 dubious results to play with.

So with that I'll move on.

DR. CURWIN: Doctor Hamey.

DR. HAMEY: Thank you. The reason for having exposure data is to be able to complete regulatory risk assessments to ensure there's a sufficient margin of exposure between the likely exposure and the toxicological end point of concern. Obviously there's a need that we have to do this consistently with a degree of confidence in order to protect the health of workers while permitting products to present acceptable risks into the market for the benefit of growers and industry. I think we'd all agree on that.

The question really then becomes, can this be adequately achieved with the PHED database? To which I

think the answer is, not very well. For two reasons. The first is the structure of the database and the algorithms it uses to estimate exposure which reflect the fact that many of the original data come from studies where incomplete body parts were monitored. As a consequence this does not provide an understanding of the distribution of individual exposures so it's not possible to characterize a particular exposure statistic and the competence associated wit that value. This is true for both central tendency and higher exposure values which are both of interest in the risk assessment. I think the AHED software does represent an opportunity to correct that, those problems.

The second problem relates to the actual data within the database. Having had personal experience with the PHED database and having for a number of years also been involved in a European project to build a similar database of studies relevant to European use, which was the Europone project that John Worgan mentioned yesterday, the deficiencies in the data I think are a serious concern. Because they fail to come up to modern standards there's actually an imbalance in the data quantity requirements on both sides of the risk assessment equation. Similar deficiencies in the hazard, i.e., the toxicology data, would not actually

be tolerated. Also, comparable shortcomings are not tolerated in other human exposure data and here I'm thinking of the residue data in treated crops that we've used in a dietary risk assessment.

The limitations have been I think correctly identified by the EPA and the issues that I believe are of particular relevance include the fact that a number of studies did not use representative workers, some of them were company employees, some we don't know actually what their employee status was. A number of the studies are only monitored for short durations and this was, as we've heard, a particular point that was discussed as a limitation during the development of the OECD guidance document on occupation exposure measurement in agricultural settings. And this causes considerable uncertainty when using the data for exposure assessments representative of real practice where workers work for a whole day.

Some records in the database have missing parameters so that work tasks, equipment or environmental conditions are not adequately described. This limits analysis of possible relationships between exposure in these parameters.

Pesticide product packing, application practices, handler training, stewardship and equipment

have probably shown changes in the last sort of 20, 30 years. These are likely to result in improvements, i.e., lower exposures, but as we don't fully understand what the determinates of exposure are, there may be some changes that have inadvertently increased the risk of exposure and these aren't reflected in the data.

It's also worthwhile to note that the EPA have stated that it's their desire to utilize more sophisticated probabilistic analyses in their occupational risk assessments. Indeed there's a strong body of scientific opinion with much agreement at the international level that both the variability and uncertainty in exposure assessments, if not risk assessment totally, should be transparently characterized.

An international workshop in 2003 was conveying, bringing together exposure assessors, modelers, toxicologists and statisticians to consider how to do this for pesticide users. It became apparent during the discussions at that workshop when considering case studies that developed using PHED, that the database contained so much unexplained variation which was likely to be due to the limitations in the data and mixed study protocols, that this objective could not currently be achieved.

Consequently it was concluded that more robust representative data are required to attempt to fill this objective.

So the questions is, you know, will the additional data help to address this? I think they probably will if the study protocols except and avoid the earlier issues which have, the limitations which in the current data, which appears to be the case.

I think it's important that the intention is to have monitored a significant proportion of the working day. The uncertainty with extrapolation will be decreased so we'll have a better understanding if exposure is proportional to the amount of active ingredient handled as this will be based on the comparison of whole day uses rather than a mixture, what we have currently when we try to make this comparison of whole day and short period uses.

Now it's extremely important that the new data are representative. This will be achieved in part by ensuring that farmers and growers are the subjects. There's also a need to understand if the sample monitored reflects the variation that occurs in reality in this population and to characterize the associated uncertainties with this sampling and to understand if they produce any biases in exposure. I think this is

an issue which we will have to consider further tomorrow.

An aspect that does not appear to be addressed satisfactorily to my belief at the moment is the issue on intra-worker variability. And I think there is a need to explore this aspect further.

Regarding the selection criteria proposed to the existing data I'm reasonably satisfied with those. I did have a question about the use of PPE in old studies but we heard yesterday that it was being looked at by, in comparison to today's standards. That was answered for the AHETF but I think a similar question is also relevant to the AEATF which I didn't ask yesterday.

And while on the subject of the AEATF criteria, I note that they state that inhalation will only be considered if applications generate what they've defined, what they've called inspirable aerosols but they haven't actually defined what those are and I would have a suspicion that they may not include inhalation monitoring as a criterion when I think it may be required. And they should also remember that although large droplets and particles may not respired, they may be deposited in the nasal region or in the mouth and they may be available for oral

absorption, they might form part of the absorbed dust. Thank you.

DR. CURWIN: Who is next here? Doctor Kim.

DR. KIM: Most of my comments have been addressed by other members of the panel so I'm going to focus on a few comments that may be helpful.

In general I'm in agreement with the EPA's conclusion that additional data could improve significantly the Agency's ability to assess workers' exposures.

However one area of great data need is documentation of task and activities as well as meteorological, physical chemical conditions, meteorological conditions which can really affect your exposure estimates. And we know from pharmacokinetic that relate exposure and dose relationships, that exposure variables are, exposure estimates are very, very sensitive to being able to predict what the internal dose is. So the database could, somebody who is querying the database should be able to extract information such as the intensity of exposure, the frequency, identifying the duration of exposure, as well as other meteorological factors that could affect exposure.

Second comment is again directed toward EPA and the AHETF has identified this already, and the EPA should I think move toward a similar approach which is to standardize the use of patches, specifically the location of the patches. Using an approach that relies on the skills and observations of the researchers who are collecting the data introduces many biases, based on the skills of the researcher and results in a lack of consistency across the studies. So a movement toward standardizing the location of the patches would be very helpful in comparing the exposures of different exposure scenarios as well as compounds.

With regard to the two databases, AHETF's database, my main comment has to do with the monitoring duration. The Task Force says that they want to focus on studies that have measured dermal exposures for which the individuals or the workers were exposed for at least half a day. This may be a little too stringent. And I understand the limitations of the analytical limits of detection, the high limits of detection as well as, well, inconsistencies in the laboratory. But with regard to high intensity and short term dermal exposures, if we set a criteria that says that we are not going to consider any studies beyond half day worker exposure durations then we're

not going to be capturing those short term, high intense exposure scenarios.

With regard tot he AEATF database my comments are directed toward the biomonitoring studies. The point is made that extrapolation parameters must be available for the study to be selected by the AEATF and a primate dermal absorption data is listed as one of the types of data that will quality for inclusion by the AEATF.

However there is a paucity of studies that have human relevant extrapolation factors and most are estimated from rat and porcine models. And you can refer the work done by James McDougall and Jim Riviera, et cetera. And maybe we'll talk about this later on, but in terms of being able to predict that amount of chemical that is deposited on the skin that actually is absorbed and penetrates the skin, there are other alternatives that Doctor Appleton spoke of, mainly using the fixed law of diffusion. And using these models allows one to be able to extrapolate from rat and porcine data to human exposure scenarios. So there you go.

My last comment has to do with the percent absorbed, and this is related to my previous comment, and it just seems that percent absorbed dose is going

to give you some wrong answers because the percent, application of that percent absorbed dose is really dependent on the dermal exposure, the level of loading on the surface of the skin. And this is because of the differential surface tensions of the skin as well as the media that is placed on top of the skin.

So what happens is that it's the first layer of skin that is most important for predicting absorption and dose. And as you have more loading on top of the skin of course you're going to get lower percent absorption. Therefore using something like the fixed law of diffusion which treats the skin as a single membrane and describing that absorption and penetration process using permeability coefficients which are readily available from these dermal absorption studies, it's just a different way of analyzing the data, may give you better estimates of the dermal, percent of the dermal dose that has actually been absorbed. That's it.

DR. CURWIN: Doctor Popendorf.

DR. POPENDORF: Well, to some degree I agree that we've made, some of my points are, have been discussed earlier. But I'm going to try to talk about the issues of the quality of the existing PHED data and the nature of why it's probably not well characterized

in terms of its limitations. And I think both groups have, particularly I guess the EPA presentation has given many examples of why it's limited, but I think the biggest problem and the focus of what I'm going to talk about is that, like the output in terms of, sort of the printout or the results of using PHED, the user is realy not given any, or the appropriate measures of quality. Basically we've got your grading which is only one, or is based on only one parameter. And even that I think I'm going to talk about some of its limitations, so that I think overall, although subjectively I think I would agree that the data is limited and should be expanded through the proposals that have been made here, but that we add a measure of quality or of a broader measure of quality so that you can actually show improvement and show the value to any user, including the human effects people of why this data would be better or be able to quantify some of the limitations.

I think as an example of the kinds of things that are not part of the grading system that have been mentioned here so far, the incompleteness of some of the body parts within any given scenario. There is really no measure of that in terms of output and that certainly should affect grade or the quality of the

result that you get from that. The number of non-detects, now that's being built into the new protocol. That could be an output of both the new and the old protocol because the example that was, just sort of came out in our, in the presentation of our information of the gloved and un-gloved hands, clearly the data is biased by that non-detect issue. And unless you had some intuitive way to look at those numbers there's no indication in terms of the, like a grading mechanism that would help to tell you that.

The short time periods, the limited or limitations in the range of the active ingredient handled would also be potential additives to that grade. Certainly if the intent, eventually one of the other questions that we'll talk about later is the linearization of the data through the use of the active, amount of active ingredient handled. And if that's in a very limited range, if the validity of that assumption has not been tested, that should be part of the grade.

The only real part of the grade that's in there right now is based on the two parameters separately. If you want to bring up that first figure I'll get an example of a couple of things to show you graphically of what this, what I'm going to be talking

about. This, okay, the top figure is basically the existing grading scheme based on the lab recovery, the percent lab recovery and the coefficient of variation for the lab recovery. And as you can see right now you're putting in for instance an A grade, has to be within a single limit set for each of those two parameters.

And if you look at it from a broader perspective, well what affect does that have in terms of the potential error if you will or the projected standard deviation of the result? What I've presented in the bottom figure is I think a better way to look at it of looking at basically the affect of the coefficient of variation as a measure of precision, divided by the percent lab recovery as a measure of accuracy. And the lower that percent recovery, thank you, the lower that percent recovery, the more of an affect it has on the coefficient of variation. So for instance, this single point, the limit for an A grade as presented is right here, is what I've presented is again the same kind of figure but everything below the red line has a probable error, what I'm calling a probable for lack of another term, probably standard deviation or whatever you might want to call it, of a multiplier of 1.17. So I mean you're looking at

basically, if you want to think of it as a percent, a 17% probable error, a probable standard deviation is an A grade. And if you think of that in terms of all the uncertainties and variables that we've been talking about today, this is like the gold standard, I mean it is, you know, very, very precise and in fact overall by adjusting for the recovery it's also very accurate.

Similarly the B grade, et cetera is shown here and you can see where the D, I mean without having looked at it in this perspective, the difference between the C and D grade is simply based on the recovery efficiency for the same coefficient of variation.

So, you know, great concept and I think, you know, the idea of having a grade, A, B, C, D, that's good and that's simple and it's intuitive, it's certainly part of the data that goes into, or the, part of the data set that goes into the PHED, it's not, well, you can only select on it as an output which limits the numbers. And we talked about, I think you gave some good presentations of the results of, of what if you just want A and B grade you end up with some losses. But I think you might want to look at expanding the definition of that grading scheme to include some of these other parameters.

I think on the next figure no, let's move on to the next one, we don't need to talk about that now.

Well I guess we'll, I'm going to talk about these points later in other discussions but I think the point here really is that the A, B, C and even the D grade data that you have, when you look at it going back to that first slide, the overall accuracy, I mean the worst grade you have there is a D factor which is a 55% variability in that data. And that's, if that were the only parameter that you used it looks pretty good in comparison to everything else.

I mean I think the thing that you really want to think about then is to go back to what I was saying earlier, to include issues of incompleteness, of the fraction of non-detects and the short period, adding that to those parameters that would allow it to be graded which would show the poor quality of some of that data, allow it to be used more effectively but I think also justify the addition of better data that is going to address all those issues that have been proposed in these two, by the two task forces.

DR. CURWIN: That's all the comments from the associate discussions for this charge and I would like to open it up to the rest of the panel for any

comments that they may have.

DR. PORTIER: Doctor Landers.

DR. LANDERS: Thank you Mr. Chairman. I have a few comments regarding what I regard as the limitations of the database and how I would suggest they could improve. Understandably they're all to do with application technology.

And so for example I feel that there is a lack of information on different types of application equipment. While a growing number of farmers and growers are in the fortunate position of owning new types of sprayers, there are a lot of antique tractors and sprayers in use. The dilemma for you of course is to which example do you use for the study tests. What is a typical sprayer?

Let's take an example, in orchards sprayers range from modern tower sprayers which direct the spray in a horizontal direction into the canopy. These are much favored by researchers, through to the traditional air blast sprayer which sprays the spray plume upwards and outwards, contaminating not only the trees but the neighbor's trees that is, not the target tree, the tractor and everyone else in the next county. It then moves to low volume atomizers and if you listen to some people in some universities there's a great trend

towards low volume atomizers. Therefore I suggest that a single study test, if for example you choose air blast sprayers this is not typical and it fails to address the concerns that I have.

Therefore my recommendation in this case is to categorize application techniques and test accordingly. And this could be applied to various other crops, not just apples.

The second area of my concern is that there's a dearth of information regarding the protection offered by engineering controls. It is now over 20 years since the state of California introduced legislation concerning closed transfer devices. And in the mid-80s there was a little flurry of research coming out of California from UC Davis, looking at their effectiveness. But not much since. And we would really like to know that for one reason which I'll come to in a moment. Induction bowls for example which are mandatory on all new sprayers in Europe, not yet here in the U.S., offer great opportunity to reduce risk, filling the sprayer knee high rather than clambering onto the tank certainly reduces potential contamination to the operator and decreases potential for environmental pollution.

Why are we interested in this? Purely

because the question exists, if we can introduce more engineering controls, then can we reduce the amount of PPE that is required? Whilst on a nice cool day like this in Washington, D.C. the thought of wearing a Tivex suit is far away but in the hot humid days in the deep south I understand it's quite unpleasant to be spraying in midsummer. So we must be aware that if we can engineer away the risk it would help us reduce the earing of these Tivex suits.

The third area I have concern with is a point that I alluded to yesterday and that is the condition of tractors and sprayers. Yesterday I mentioned tractors and how in our research at Cornell we've seen contamination of the operator's clothing due to the fine quality of the tractor seat. This is even of more concern where you have custom applicators using self-propelled sprayers who may spend 18 hours a day climbing in and out of cabs wearing contaminated clothing.

The condition of the sprayer is an area I'd to address today. Many surveys have shown sprayers to be in poor condition. Research shows that sometimes the outer side of the sprayer is as contaminated as the inside of the tank. There are ISO standards available concerning the tank cleanliness and I would recommend

the adoption of these standards as part of good practice. Study tests are conducted on an "as is" basis. They take the sprayer "as it" on the day of its operation and off they go. GLP is followed in the laboratory but what about the field? Are we starting off with a vessel that is contaminated? So for example, we put our operator in a dosimeter in some nice clothes and he immediately, he or she immediately lean over this scruffy sprayer and contaminate a dosimeter with product that may have been on there from yesterday or two days or whenever.

So new technology does exist. For example, low drift nozzles, air induction nozzles reduce drift considerably, not only from the target area but also contamination of the sprayer. So if we started off at base one with a clean sprayer I would recommend this as good practice for the tests. Thank you.

DR. PORTIER: Any additional questions? Doctor Johnson.

DR. JOHNSON: Well just a comment. Part of my career has been involved with coauthoring three books in statistics called, Analysis and Messy Data, Volume 1, Volume 2, Volume 3.

The data in the PHED database is messier than I'd want to include in any of those books. So the

point I want to make is the main thing that we're, that I think we're after is trying to predict risk and what's the relationship between what's observed and how does that relate to actual risk of the individual being measured?

And it seems to me that based on the data in the PHED database, given the problems that it has, that it makes this idea of trying to predict risk a very, very, very tough job and I think there is a need for new data and I would support the collection of that.

The second point that I wanted to make, I don't know whether this is the right place to make it, but it did ask about the way that the studies are being graded in terms of quality and that has to do with the coefficient, the way the coefficient or variation is measured. It seems that if the data have the lognormal distribution, then coefficient of variation maybe should be measured in terms of log units rather than in terms of the raw units. And I don't know where that, I can't tell for sure whether that's being done and where it's being done, but I would make that recommendation. That might be something that you'd want to do.

DR. PORTIER: Doctor MacDonald.

DR. MACDONALD: I think Doctor Landers' remarks were very interesting but I think that also

takes us off in a direction that we were really not asked to go.

And that is answering the question, does newer equipment substantially mitigate risk? I think that's a very important question.

But neither database that we're, the existing one or the ones we're looking at proposed are intended to answer that question. I think that's, that would require a completely different kind of study.

DR. PORTIER: And I guess I took his comments as being recommendations for additional information to be gathered at the time that these studies are done. Because if I remember correctly there's not a lot of equipment specific information in the scenario metadata.

DR. LANDERS: I agree with the Chairman.

DR. MACDONALD: Yeah, my concern though is that we're not going to get enough data from specific types of equipment to be able to make good use of the breakdown. We'll have another covariant in there but we won't have enough information to make use of it.

DR. PORTIER: And I guess, again I took his comments as something we're going to reevaluate in question 5 when we talk about study design issues as it relates not only to sample size but variability. And I

think you're, in that context the scenarios and what goes into describing a scenario is part of the equipment issue.

Yes, Doctor Barr.

DR. BARR: I'd like to speak a little bit about the issues that Doctor Popendorf brought up about data quality. And I think that you're moving in the right direction by trying to generate more data now because, not only has the farming technology and our ability to design studies improved over the last 20, 30 years, so has out ability to detect the chemicals in the laboratory as well.

And so when you're going to talk about grading studies, the European Union actually has a system for grading them based upon their ability to confirm a chemical, a particular chemical for analysis and criteria about CVs and spiked recoveries. But I would think if you were going to collect new data that you would try and set a systematic guideline for levels where those data are collected because a CV can change as you go down lower in the level of detection. And so I think that these need to be standardized if it's going to be used as a quality criterion for grading studies.

DR. PORTIER: Doctor Hines.

DR. HINES: Well, I just wanted to add, I think one of the objectives in collecting new data is to better characterize our distribution of exposures. And for that purpose that's one of the reasons why there's a focus on getting a good range of amount of chemical use. And I think that also addresses why we want to see different types of equipment, because we may have some modern equipment designed to minimize exposure at the low end of our distribution but I heartily second your observation that we still have some very antiquated methods out there of applying pesticides in orchards. And that it may take some outreach to try and find those people who are doing those methods. And so we can get a better distribution and that may be the amount, it may be the equipment and there may be some other factors.

DR. PORTIER: Doctor Lu.

DR. LU: I was waiting for someone to bring up this issue so I don't have to provide a written statement, but

DR. PORTIER: You still have to provide a written statement.

DR. LU: I guess the missing part of this discussion is that both the Agency and the task force group kind of shy away from collecting additional

biomonitoring data. There are disadvantages that were presented by both parties in terms of, you know, the difficulty to do these kind of studies. There's a Human Subjects Review Board barrier they have to cross. I don't think those are the good reasons to not doing this type of work. And especially the issue related to the Human Subjects Review Board. I think their establishment is to help us to conduct robust human studies, not to prohibit us from doing this type of work.

As a matter of fact, I think people brought up European countries, I went to Warsaw a couple of months ago and I heard that they are going to set aside a huge chunk of money and then come out with an organization that deals with conducting biological monitoring studies in the European countries. So we, again we're far behind on this part.

Another ironic situation is that both parties identify the lack of pharmacokinetics and so and so forth, but both parties also provide data that shows that we're able to calculate the absorbed dose using biological data. Don't you think that's ironic? If you don't have the pharmacokinetics how can you do those calculations?

So again I understand the limitations but

since we're talking about what type of data is needed in the future I think it's almost impossible to ignore the importance of biological data. Now I have to write a statement.

DR. PORTIER: Alex, you know, when I look at what we're talking about here a lot of this is tier 1 and tier 2 type studies and wouldn't you think that the biomonitoring study data is going to pertain more to these tier 3 kind of studies where there's much more need for that?

DR. LU: Well as a matter of fact I think when I was in the school I was taught that you should take the biological data first. If the level looked okay that means everything is fine in the field. If all of a sudden case A has such a high level then you want to know what happened. And that's why you conduct a dermal exposure assessment or inhalation, to find out the reason. And now we're going backward and going backward in a way that you don't even have a rear mirror so chances are you'll have an accident.

Anyway, it's very easy to do a biological monitoring study in an occupational setting because they tend to expose higher, the chances are we'd get a much better limit detection. I don't know about other people but I have a very limited field experience, I

think Cynthia Hines may be able to comment on this, that workers tend to be very cooperative in these types of studies. So I don't think there's a lot of logistical reasons that are put out by both parties are legitimate in the sense that, you know, based on our experience.

So I would say biological studies might be the tier 1 study, not tier 3.

DR. PORTIER: Doctor Chambers.

DR. CHAMBERS: This is Jan Chambers. Let me just clarify about the Human Studies Review Board. This board will be looking at all studies that are involving intentional dosing of humans whether it's passive dosimetry or biomonitoring, regardless of what the end point is.

DR. LU: This is Alex again. But the question is, what is intention dosing? I mean those are pesticide applicators, with or without a study that we impose on them. They still go out and spray pesticide for making a living. That's one argument.

The other argument is that sometimes the review board looks at the exposure level and says, oh, this might pose some significant risk. But if the level is comparable to the level that those people are going to experience in the field, they why are we still

allowing those pesticides to be used in the field but not in the human control study?

So those dilemmas need to worked out in the human subject level, but we should not be discouraged from doing this type of work. I mean it's part of our work to commicate with the Human Subjects Review Board but, you know, that should not be used as an excuse not to do biological monitoring studies.

DR. PORTIER: Point taken. Doctor Curwin.

DR. CURWIN: I have a couple of comments. One is to Alex actually. I think we can all agree that it's desirable to have biomonitoring studies but I think we need to put this into context with the regulatory agencies in that they want to develop a generic database so that they can do their exposure assessments without having to provide new data for each compound that is coming in for registration.

And I think that's difficult to do with a biomonitoring type approach because, you know, the nature of biomonitoring is you have to have chemical specific data. So while it would be highly desirable to have these, this information on each compound, if we really are, if we feel that the resources or limitations and that sort of thing that the regulatory agencies are under, and that the generic exposure

database is the way to go, I'm not sure that the biomonitoring then is going to apply here. That'll be discussed later this afternoon I do believe.

And then another comment, and I don't want to put Doctor Chambers on the spot but I'm going to a little bit, just because of your HSRB hat, and I could be wrong in this assumption. But I think one of the impetuses for this charge question was the recent HSRB review for the additional data and HSRB had said that there wasn't a clear indication that there is a need for data. From what I've been hearing in this discussion it seems like for the panel members who have spoken at least, that there is a consensus that the additional data is warranted due to the limitations of fed.

And I'm just curious because of your HSRB affiliation if you have a comment on that particular charge?

DR. CHAMBERS: Yes Doctor Curwin, this is Jan Chambers. That was one of the major concerns that HSRB had when we saw some of the protocols that were presented during the June meeting, that there really didn't seem to be sufficient evidence to the panel that was looking at that, that there was a need for new data.

And I'm just a little bit concerned actually about the fuzziness of what the goals of the HSRB are that are kind of floating around here right now. And I'm wondering if Jeff or Jeff or Bill Jordan or somebody might just give a brief overview of what the statutory need for the HSRB's activities are.

MR. DAWSON: I'll let Bill do that.

MR. JORDAN: Thanks, I'm Bill Jordan, I work for EPA's Pesticide Office and have worked with the Human Studies Review Board on their, fulfilling their responsibilities under the recently promulgated EPA regulation to improve protections for subjects of human research.

The board has a couple of different functions. The first of which is to review completed studies that involve intentional dosing of human subjects and there are different categories of such research. There are intentional dosing studies which are designed to measure a toxic affect. There are exposure studies such as the ones that we've been talking about today. And then there are things such as studies of insect repellant efficacy and so on. Not all of the completed studies need to go to the Human Studies Review Board under the regulation but ones done after April 2006 will, when they're completed and

submitted to EPA and EPA decides, yes, the data are something we want to use in our reviews, we'll send them to the board for a review. And when the board gets such studies they need to, under the charter and our regulations, give us feedback on two distinct but related aspects of the research.

The first of which is, are the data scientifically sound? And secondly, were they produced in a manner that is consistent with the ethical standards applicable to that research? For studies that have, are at the proposal stage, our regulation directs EPA to review proposals for research and once we at EPA have completed our review, to provide copies of the materials relating to these new protocols to the Human Studies Review Board and ask the Board's advice on the proposed research. Again, the Board is looking at two distinct but related aspects of the research.

The first of which is, will the data produce scientifically sound results? And secondly, will the data comply with or comport with the applicable ethical standards? And the ethical standards that apply for new research are the standards contained in the common rule and through EPA's new regulation, extended essentially comparable requirements to third party research. And so we'll be asking the board, do you

think under the common rule standards, that this new set of proposals for research that AG. Handler Exposure Task Force wants to do, do you think these studies are going to give us scientifically valid information and do you think they will comport with the ethical treatment of subjects?

So that's the thrust of what the Board is being asked to do.

The last thing that I'll mention is that on a case by case basis we at EPA can say there's some other questions we'd like to get the Board's advice on relating to the conduct of human research that may not focus on a specific study, either a proposed study or a completed study.

DR. PORTIER: Thank you. Doctor Hamey.

DR. HAMEY: Thank you. It was just a minor comment to what Doctor Curwin was saying in response to what Doctor Lu said. And regarding the use of biological monitoring as a sort of preferred approach to assessing exposure.

My understanding is a lot of the assessments the EPA are trying to make are before products are actually approved and allowed onto the market. So, you know, predictive estimates of exposure, so in order to decide whether it is acceptable for it to be used. So

there's a Catch 22 dilemma.

DR. PORTIER: Doctor Popendorf.

DR. POPENDORF: Yes, Bill or perhaps Janice, but I was caught by the phrase, intentional exposure, and to what would seem to be an interpretation of what intentional means, intention to expose someone who would not otherwise be exposed. And in this case or cases of air pollution health effects where people are being exposed, the issue of intentional exposure would seem not to apply. Is there another category in that evaluation or how is that being interpreted?

DR. PORTIER: I think we can have EPA's input on this.

MR. JORDAN: Okay, this is Bill Jordan again. The regulation applies to human research involving intentional exposure of subjects to a pesticide and there is a definition of intentional exposure. And it's perhaps a bit broader than you may be thinking of, Doctor Popendorf, and certainly we've had other people raise similar questions.

For purposes of the regulation, intentional exposure is defined to mean exposure that only occurs, that would not have occurred but for the person, the subject's participation in the research. And so let me

see if I can give some examples that might clarify how we at EPA think of the distinction. And I'll concede at the outset that there will be situations that'll be a gray area and will need to be looked at on a case by case basis.

If someone says to a subject, here, participate in this study and we're going to apply some chemical to your skin to see how much of that chemical crosses the skin barrier and we can then measure as a urinary metabolite. That's an intentional dosing study.

On the other hand if the researcher goes to a field and collects urine from people who are hired by a farmer completely apart from the research, gets consent from the participants and measures urinary metabolite levels, that would be an observational study.

The difference between those two situations is that the exposure experienced by the subjects occurs in the first instance as a consequence of participation in the research. In the second instance it's a consequence of the subject's voluntary choices about whether to go to work and what kinds of pesticides to use or his employer's choices about that.

There will be cases that are somewhat in a gray area but the kinds of scripted activities that are

called for in the AG. Handler Exposure Task Force protocols are ones which we deem, put it on the side of being an intentional exposure study.

DR. PORTIER: Doctor Chambers.

DR. CHAMBERS: I guess just to reiterate a little bit of the concerns that arose during HSRB meetings when this was first presented, is that partly what Bill Jordan just said about the scripting. There will be some, in some cases some scripting and not just absolutely regular activities. And then the other concern is that in some cases it will be surrogate compounds and not necessarily the ones I guess that were going to be used that day in the field anyway. And so that makes it kind of one of those gray area type studies I think. So sort of semi-natural but semi-scripted.

DR. PORTIER: Any additional questions, comments? I think this is probably a good place to break on this question and to take a short afternoon break. Mr. Dawson, did you get what you wanted to get out of this question or Mr. Evans? Do you guys have any additional questions that well, you can think about it. We'll revisit it after the break because I see a lot of people yawning, we need to get up and move around a little bit.

So we'll ask that question when we get back. I won't quite close the question until we get back from the break.

Let's take a 15 minute break, I have 2:40, that's puts us back at 2:55.

(WHEREUPON, there was a recess).

DR. PORTIER: Okay, it looks like we've got our panel back. Maybe I should, I almost hesitate to ask if there's any additional panel questions at this point because I really want to go on to the next charge question. But if there's a dying question among the panel I think we could consider it. Did anybody come up with a I'm not going to give you a lot of time to think about it.

Jeff and Jeff, it looks like, my take on this is I get a feeling that the panel feels that the additional data is justified. I think that's part of the take home message. The other message is that the selection criteria for the most part looks good but we're going to have a number of recommendations for additional data elements that we'd like to see recorded and some other side issues that are going to be discussed.

Is that kind of what you --

MR. EVANS: I would agree with that, we

were very happy with the answers and you gave us a lot of things to think about to enable us to press our case further and we very much appreciate that. And we are ready to move on to the next question if

DR. PORTIER: And Doctor Curwin, it's going to be interesting to see how you include the discussion on the Health Effects Committee. You asked that question.

Okay, I think we're ready to read to read the second charge question.

MR. EVANS: I'll be happy to do that. The common approach for conducting dermal exposure monitoring studies relies on the use of whole body dosimetry, hand washing and facial neck wipes. In some cases biological monitoring is also used as an alternative method. Exposure estimates and Agency risk assessments however typically rely on two of the skin measurements. For example, potential dose coupled with dermal absorption data or dermal toxicity studies in order to calculate risks. The Agency believes that these methods are complementary and that they can provide appropriate estimates for exposure assessment, but that the results directly related to the reliability of the inputs used.

Please comment on the Agency's conclusion

regarding passive dosimetry and biological monitoring, including whether a systematic bias exists in either approach.

Based on the information presented the Agency has particular concerns over three specific aspects of how these studies are conducted, including, 1, the possible need to correct for the efficiency of the handwash technique, 2, compensating for absorption of residues through the skin during sample collection periods and 3, the breakthrough of residues under whole body dosimeter garments. Please comment on the need to systematically account for residue losses due to these potential method biases. If there is a need, please describe how these corrections should be accomplished in a way that could reduce uncertainties in the resulting exposure estimates.

DR. PORTIER: Doctor Barr, it looks like there's a lot of comments. I guess you'll start us off on this.

DR. BARR: I'll start us off. First of all as a preface to my comments I'd like to say that the presentations that were given today were quite excellent and directly impact the charge of our working group. And so most of us kind of feel a little overwhelmed with the data that was presented. And so

we want an opportunity to digest the remarks and perhaps revisit some of these questions at a later date during the week.

The first question really wasn't a question but it was to ask our overall assessment of the passive dosimetry and biomonitoring data and whether there's a systematic bias between the two measures. From the information that we've been presented and given today, both from the EPA and from the task force, we don't see that a systematic bias exists.

Again we have some questions on how these comparisons were derived and would like to look more deeply into it tonight before we finalize that answer.

Since the last three questions are so closely linked and deal with the efficacy of passive dosimetry methods, whether they involve hand washing or whole body dosimeters to adequately estimate the external dose, we'll just treat them as one question and kind of try to address them all together.

I think existing data clearly indicate that for certain pesticides absorption of a pesticide on the skin or into the body can occur within a matter of minutes after the exposure has occurred. This absorption would be expected to be pesticide dependent and related to the ability of the particular pesticide

to penetrate the skin. In addition, variability in the amount absorbed would be expected based upon the time the pesticide remains on the skin prior to washing, the amount of pesticide that is actually on the skin and general inter-person variability. In addition, the ability of the solvent, and here several solvents were discussed, both alcohol, water and detergent based, to remove the chemical from the skin or promote its absorption into skin may vary based upon the physical and chemical properties of the pesticide and adherence to the standard hand washing protocols.

Most, but not all of these potential biases would most likely result in an underestimation of the amount of the pesticide present in the skin. For example, data presented in Fenske and Lu, 1994 show that several hand washing solvents recover less than 50% of chlorpyifos from the skin immediately after exposure and about 20% was recovered from the hands one hour after exposure.

Using dermal absorption factors based upon existing data such as the 3% factor based on Nolan et al's paper for chlorpyrifos should be used, although they don't necessarily reflect the various parameters that can affect dermal absorption.

I think correcting for these biases is going

to be difficult because no gold standard for comparison exists. The current comparisons that have been given to us compare biomonitoring against the dermal absorption and of course biomonitoring is not without its limitations as well. And we have to make several assumptions with biomonitoring as with dosimetry that gives both approaches some degree of uncertainty.

If correction methods can be derived that can significantly decrease the uncertainty at a reasonable cost then perhaps they should be applied. For example, the approach using the log kow that was mentioned earlier would be a possible solution if deemed appropriate and if it would have a significant impact on the overall exposure estimate.

A second approach of course which you also mentioned today would be to quantify the amount of absorbed dose based on excreted metabolites and pharmacokinetic information and add this to the passive dosimetry estimates. As biomonitoring provides data that are independent of the root of exposure, other roots of exposure would be included which might overestimate the total dermal dose. The biomonitoring approach may be difficult as well because many pesticides do not have reliable biomarkers and pharmacokinetic information is insufficient or largely

lacking for most pesticides. In addition, the burden to the participant becomes exponentially larger if 24 hour urine samples are requested over a period of days.

However, the biomonitoring approach would likely be one of the few viable approaches acceptable to estimate the amount of breakthrough from whole body dosimeters. One cannot assume that you have a uniform breakthrough from a whole body dosimeter and there appears to be no reliable way of predicting the amount of body surface affected. Also, breakthrough is likely affected by the task being performed as well.

Some tasks may have minimal potential for breakthrough in which case no correction would be necessary. But for tasks where breakthrough is likely biomonitoring would complement the passive dosimetry data to estimate the external dose. Alternatively, some sort of patch placed under the whole body dosimeter may be able to provide some breakthrough information if those patches were strategically placed.

I believe the existing data demonstrates that some sort of correction should be applied or at least the uncertainty recognized and it should be chemical dependent. One thing that has been I think of concern to a lot of the people in our working group is trying to have something generic that doesn't use the chemical

and physical properties of each independent pesticide.

Before today I had seen no study in which biomonitoring results compared so well to passive dosimetry estimates which is why in part so many studies have coupled passive dosimetry an/or other environmental analyses with biomonitoringh to estimate total exposure. Likely, in my opinion, an approach using the chemical physical properties of the pesticide and wash solvent should be employed to derive a correction factor to correct for dermal absorption of the chemical when estimating hand exposure using passive dosimetry.

Biomonitoring is also viable but a more costly and cumbersome option and may overestimate the external dose if other routes of exposure are significant or if the selected biomarker is not selected for the exposure.

Again for the data provide it's just not clear to us whether a correction factor or compensating for breakthrough is necessary. However the panel feels strongly that the chemical and physical properties of each single chemical should be considered as a part of this generic database. We don't know from the data presented whether the agreement would hold if sorted by individual pesticides for example.

Also we think some attempt to include the studies that were excluded in the study presented by the task force should be done and clearly if some correction factor is adopted it should be chemical dependent.

I'd like to I guess invite the other associate discussants to give their opinions as well.

DR. PORTIER: Doctor Hines, Cynthia.

DR. HINES: Thank you Dana, that was very exhaustive, I'll see if I can find something to expand upon or add to that.

Taking the first question on whether or not there is a systematic bias in the passive dosimetry and the biological monitoring, I would concur with what Dana said, that given the data that we have been shown by EPA and by the Agricultural Handlers Exposure Task Force, as presented the data do not seem to show a systematic bias.

I do have some concern that there may be bias within individual chemicals. We haven't much time to really look at that. For me the implications of that extend to maybe new chemicals down the road or chemicals that we do additional biomonitoring on where we may learn something new about the relationship between passive dosimetry and dose through biological

monitoring. And I would hope that in the future if EPA were to come across a study that had concurrent biological monitoring and passive dosimetry, or one of these sequential studies and there was an obvious, in particular the passive dosimetry underestimated the biological monitoring that EPA would maybe take that into consideration and look at that and not just simply take what was in the database and ignore that and maybe that's your routine procedures.

The next question had to do with the possible need for correcting for efficiency of the hand washing technique. I think the challenge in that question is the word, need, versus the word, feasibility. Clearly there is quite a variation in the efficiency of removal in these hand washing techniques as we've seen from the data from substances that are recovered with, you know, in excess of 90% efficiency and then substances like Dana mentioned, chlorpyrifos that are less well recovered. And this may have a lot to do with both the techniques that were used in the studies and also the solvent systems, contact times, those kinds of things.

So having said that it would seem that in a sense when you have poor efficiency of removal that it would seem that you would need to do some kind of correction, although when I start thinking about the

feasibility of actually doing this and extending this across chemicals it becomes more problematic. Also, factoring into my thinking is that at least under the proposed Agricultural Handlers Exposure Task Force studies, participants will all be wearing gloves. And so hand loading may be very low to start with. And so the whole impact of this removal efficiency may really be not a significant element.

So I think on balance I'm not feeling that that is a, the correction is something that's highly needed. It might be, you know, when you're exploring data something you could do would be to see what if we corrected our doses for this, is it going to make much of an analysis difference or sensitivity difference in the whole body versus the dermal, those kinds of sensitivity analyses?

On the second question, absorption of residues through the skin during the sample collection periods, as Dana pointed out this is going to be highly chemical dependent and it's going to be dose dependent. And so there's a lot of factors in there. You know, I think my general impression is that probably that contribution to exposure will not be high and so I tend to think that probably there's not a great need for correction there as well.

Again I would hope that if EPA for a particular chemical as it is being registered or re-registered really shows an obvious deviation from this where you think that it's going to affect the whole risk assessment, that you would take any other data into account.

And finally the breakthrough of residues under whole body dosimeter garments, you know, what I'm most familiar with is, you know, when we do air sampling in industrial hygiene we always have a backup section and we can on every study know whether we've got breakthrough. And it's a technical challenge that we don't have that for whole body dosimetry or even for patch dosimetry, whereas we're conducting these studies to know whether or not we've had breakthrough. And if anyone could ever engineer a suit or a patch that would allow us to actually measure that during our sampling, that to me would be the ideal situation. So that we would know on a case by case basis whether we really needed to correct.

And as Dana pointed out the dilemma with breakthrough is that with pesticides you don't get this nice uniform deposition. You could have, you know, a leak along the sleeve and it gets saturated so you might have a breakthrough in one spot but not in 90% of

the rest of the garment. And I don't honestly know how you would deal with that. We discussed this possibility and maybe others have done this of selective patches that act as monitors underneath the dosimeter. So perhaps that could be explored or maybe has been discussed. But in the absence of any real sound way to do this I don't think that I would advise making that correction.

The one other comment I would make is this idea of maybe looking at the optimal water partition coefficient and its relationship to the removal efficiency, I thought was intriguing. There isn't a lot of data in there. That might be worth pursuing to see if you can, you know, get more data, I don't know if that's going to bring in human subjects issues, but of the different approaches that were suggested for looking at this problem of handwash or hand rinsing removal efficiency, that one to me seemed the most interesting.

DR. PORTIER: Very good. Doctor Hughes.

DR. HUGHES: Again I'll make my comments brief because I think Doctor Barr has pretty much done a good job of covering them. I'll also iterate what she said that we appreciate the industry's as well as EPA's efforts in giving us some comparisons between

passive dosimetry and the biomonitoring. The way I have looked at this is basically putting it into more of an epidemiological perspective and that is not uncommon when you conduct a case control study to look at the biases that impact the study to determine the nature and the magnitude of their affect on the result. In other words, if it overestimates and how much it overestimates. If it underestimates, how much it underestimates.

And then with the effect of looking at whether the result you get is generalizable. Okay, we've often mentioned the term accurate but I think it's more applicable for regulatory purposes to use that term generalizable. In the same way we have to look at the end result with regard to all the parameters, how they're going to overestimate and underestimate the possible results that you would get from any model that you have that predicts a risk.

When you look at the comparisons between passive and biological monitoring you see that the variability is an order of magnitude off, in my experience I agree with the Agency that that's acceptable. And so I go on and have to take a look at exactly what would hand washing mean and what are the variations? And I appreciate the industry's evaluation

of looking at risk assessments and taking a look at exactly what I would regard as a sensitivity analysis, looking at each one fo those parameters and figuring out the variability in each one of those parameters and how much it would make a change to the overall result.

For the AHED database where actually one is using gloves and protecting the skin the dermal exposure on the hands is probably not as significant as it would be for other exposures, being the Residential Task Force or the Reentry Task Force. In studies that we had and the reentry study on blueberries that was mentioned by Doctor Olsen, we find that 50% of the exposure occurs on hands. And certainly that's not to be expected in AHED. And certainly with regard to looking a the model in more of a probabilistic determination one wouldn't expect that there would be much sensitivity to variations within looking at the efficiencies in hand washing and absorption thereof.

Nevertheless, when I say that I'm still a little bit concerned that looking at the possible need to correct the efficiency of hand washing techniques might be valuable in other situations. Again, where the hand is unprotected, where you might be in the agricultural, might look at the Agricultural Reentry Task Force data or the residential data, where hands

are unprotected where you might be dealing with young children. And I think that there is, as Doctor Barr suggested, some cause that we'd go ahead and take a, and look at the data and make the, and look at Doctor Fenske's data and assume or at least think that there is a probability that you're underestimating the estimate.

And to go ahead and find ways of compensating for that based on some biomonitoring data.

And so I just wanted to add some comments with regard to acknowledging the sensitivity based on the probabilistic study, but also saying that there might be occasions where we really do need to look at that and we can't quantify exactly what the absorption efficiencies are from the information on hand and we really do need to go one and look at a more comprehensive study, looking at not only the components, the kow's, we'll have to look at the concentrations, we'll have to look at the timing.

And also we have to look at the various protocols and make sure that what we're emulating with regard to biomonitoring with regard to whether it's a dried residue on a plant or actually direct application with the different formulations, that we have some comparisons there as well.

DR. PORTIER: Doctor Kim.

DR. KIM: So some of the biases in hand washing patch samplers and whole body dosimeters, they've been discussed by other members of the panel and they've been fairly discussed, thoroughly discussed in the literature so I won't really comment on them. But my only recommendation is that the uncertainties associated with each of the sampling techniques, they just be stated up front, they be incorporated into the databases and just, yeah, so it's stated. So not necessarily at this point correcting for any biases because there is, like Doctor Barr said, there is no gold standard to compare against.

My, most of my comments are going to focus on skin biology. You know, we've focused on, it's been said in the past that physical chemical properties of the exposure scenario are most important for predicting dermal, or measuring dermal exposure and predicting the internal dose that results from the dermal exposure. But I would argue that some of the skin biology or consideration of the skin biology is very important because if you look at an inhalation exposure study, a chemical that enters the alveolar region and it crosses that alveolar lining, it's, the diffusion is very rapid so it's not a diffusion limited uptake for inhalation

exposure to chemicals.

But for the skin, the skin is a very dense layer, it has all sorts of cornified cells, proteins, lipids, and this very messy matrix will affect how chemicals are absorbed or taken up into the body. So that in the skin sometimes what happens is that the skin holds on to these chemicals for fairly long periods of time. And understanding how the chemical behaves inside the skin is very important and this is very relevant, I mean it's been discussed fairly extensively by the FDA and in the pharmaceutical industry. So a patch dosimeter that better captures the level of chemical that is as close to the skin as possible is preferred. As well as when you're choosing or selecting the patch sampler it should have some characteristics that are similar to human skin. And there was a recent publication that came out of the IOM where they invented a sampler that had a charcoal backing and various layers that were able to better mimic uptake via the skin.

As for any of the residues that are, that result from breakthrough across a sampler, the EPA doesn't really talk about tape stripping which is a method that has been used by the FDA and pharmaceutical industries extensively to actually measure the chemical

concentration or the amount of chemical in the stratum corneum. And through successive tape strips you able to actually get at what the dose is and what the time course behavior of that chemical is within the stratum corneum because that's what drives ultimately what, how much of a chemical goes inside for systemic circulation.

The other comment has to do with the percent dermal, dermal absorption factor, And it's been demonstrated that this varies from the location of the, by location on the body. So for example a dermal absorption across the hands is going to be completely different because of the physiology of the skin relative to on the eyelids for example. So I think that is going to contribute to a lot of the uncertainties and there are techniques in place right now that do take into account the thickness of the skin at different layers for examining differences in the percent dermal absorption.

DR. PORTIER: Doctor Lu.

DR. LU: I think the question that's set out for the panel has been discussed thoroughly. I guess I kind of set a tone when I, you know, answered the question of the data needed that, you know, just stay away from this complicated dermal exposure

scenario and focus on something that may give you a better quality of the data. Those three questions are very significant.

And I want to echo the example that Cynthia Hines raised is the air sampling tube. There is the back end that will absorb the breakthrough. And as a matter of fact if I can recall, if you found 30% of breakthrough in the back part of the sampler, that whole sample should be tossed away because you can see that it's an invalidated measurement because you don't know how much actually got out of the tube and is not being absorbed.

So in the case of whole body dosimetry, first of all we don't know whether there's a breakthrough or not. If there's a breakthrough then we have to throw the sample away. And you can see that we're only generating one dosimetry sample per subject. That's a very valuable sample. If you throw it away then you've got nothing. So that's a significant limitation. Breakthrough usually results from excessive exposures and then you just throw away a very high value of the number. Again that's something that you can never justify, you can never compensate it.

A lot of issues in terms of correction of the efficiency of handwash, the compensating absorption,

once we modify the skin integrity or based on the observation and a good guess, but we don't know how to compensate that because again it's very complicated. EPA actually is asking multi million questions. It can be resolved but how much money are you going to put, set aside to answer those questions? So again, those are just the discussions.

I think throughout the exercise of using the PHED data by EPA again we, you know, we can see that a lot of points that we try to study in terms of the agreement and so on and so forth is just not there. The reason it's not there is partly because of the quality of the data, but also it's because the nature of studying dermal exposures. Did I make sense?

DR. PORTIER: At this time we'll open it up too the panel. Any comments? Doctor Handwerger.

DR. HANDWERGER: It's just an obvious comment that the skin is more than just a filter. I mean it's not just a place where things go from the exterior of the body into the circulation. The skin certainly acts on a number of substances to change them biochemically and certainly things can have affects locally at the skin level. I think we're all aware of the role of sunlight for example on the metabolism of vitamin D and things like that. So I wouldn't just

think of skin as just a filter that doesn't modify things along the way. It may, certainly it may have a role in the metabolism of these things in addition to just how rapidly they get into the circulation.

DR. PORTIER: Doctor Popendorf.

DR. POPENDORF: Yes, I'd like to comment and sort of explore a couple of small modifications to what's been said.

I mean I think the first point is the issue of the bias and the statements have been made that there is no bias. And I think there's other evidence from other studies that weren't presented that suggest there could be a bias and I guess just the nuance here is that we're not able to detect a bias would probably be a better statement. There's just a lot of noise in the data and if it exists, clearly it's much smaller than all the effects of other variables that aren't being controlled.

The second point in terms of the compensating for absorption residues, I think a better word might be adsorption because I think it's really adsorption going on in the skin in terms of trying to do a wash to recover it, not so much whether it's absorbed and goes through the rest of the body, but it's retained by the skin, presumably eventually either to be as point out

by the skin model, it'll retain for maybe a long time, eventually some of it will be sloughed off, some of it will perhaps be washed off, some of it will be absorbed. But it, from a passive dosimetry perspective adsorption would keep it from being recovered in a wash.

And I think there's some good evidence again that suggests that it happens perhaps. Of course it varies with the chemicals, those that have been studied may be a factor of 2, 50% reduction, time dependent. I was playing with some of the data that's presented in the review and it, and you've got two points, you know, the immediate recovery and the 1 hour recovery. And if you assume an exponential retention model you get a, you know, of course you can draw a line through two points, any line, it turns out that the lines are characteristic of the KOW of the two chemicals. So I think it suggests that a model could be developed certainly that fits those two. The data that's available, now that's one dose, you know, immediate recovery and 1 hour later if you tried to apply that to real world scenarios you'd have to make some assumption of the time history of whatever you recover. And if for instance if you assume a uniform exposure over whatever that exposure period is, 1 hour, 3, 4, 6 hours

you're going to see two things.

One, you're going to see a lot more retention of that early dose so you'll need to do the integration basically of that formula. And I think if you work that out the way the numbers are going to come out, what you'll also see, people have commented that there's an equilibrium being reached, and I think again a better term there would be a steady state in terms of the dosing rate over a period of time, assume it's a constant dosing rate, retention's going on at a period of time and eventually you'll reach a point where you're only going to get off a certain, a fraction, a constant fraction of what's been deposited over time. That's the way the math would work out on that.

Let's see, I think a couple of other points here, one, we also looked a bit at, there was data on the wipes and I'm sure if wipes are being proposed as part of that new protocol but I think we really haven't commented on wipes per se, but I think there is a much stronger bias from a wipe than either the wash of a passive dosimetry and I don't think we would recommend wipes which kind of complicates a bit the face and neck assessments. But I think it would certainly be my recommendation and maybe we can look for some consensus whether that might be taken as one category that there

probably is a significant order of magnitude bias because not only are you having retention but you're not getting good mechanical recovery.

The last point I'd like to make is going back to the figures that I have up there. Looking at the issue of whole body dosimetry versus patches, I've been, I've used patches in several situations beginning with harvester data and I think one of the key aspects there is you can assume very uniform exposures. In applicators I don't think you can make that assumption and I think there are some limitations with patches.

Let's see, if we go on to the next, let's go with two more slides. I'll use this as an example. What I'm going to talk about under the next question has to do with biomonitoring versus excretion. But if you were to look at the issue of patches just as an issue of bias or performance, part of the broad question, is you look at this magnitude of the probable error, looking at the coefficient of variation in terms of coefficient of variation for patches would be the variability in the exposure on a given location, a given body part. If it isn't uniform, how variable is it? And you could put a value to that. The denominator instead of percent excretion is shown there, I'm sorry, I thought I had the intermediate one,

it's going to look exactly like this however, the denominator would be the ratio of the body area to the patch area. It's again it's a scaling factor much like excretion would be if you're modeling up from what's excreted to what the dose was or the same basic concept was applied to the denominator was recovery for the, for question 1. But in this case the scaling factor is a ratio for the body area for a given patch, to the patch area itself. And depending on the kinds of patches that are used you're looking at a 25 to 4% of that part of the body being covered by the patch. The reciprocal of that means you've got a scaling factor somewhere in the neighborhood of 25 to 50.

Now, if you have a scaling factor of, well, this is set up, the x axis here is basically the percent of the area covered, so if you're looking at 2% to 4% you can see where that is on the log scale on the x axis and even small amounts of variability in the dose is going to give you rather large variations in the measured dose. So I think the conclusion here if you hadn't already come to it is that patch monitoring for spotty exposures that might occur during application is probably not recommended. Or if you're going it you're going to see a large amount of variability in that data.

DR. PORTIER: Other comments? Doctor Popendorf.

DR. POPENDORF: I'm just looking at my notes. There were some other data also that I suppose could be an exception to what I just said. If for instance you're looking at a protected area where the exposure, once it goes through the barrier, for instance gloves or perhaps an enclosed cab where you're not getting spotty exposures you can make a much better assumption of uniformity which might get around this problem.

So there may be a few exceptions where patches would work, but in general what I said earlier is that I wouldn't recommend them here.

DR. PORTIER: I have a question of Doctor Barr or Cynthia. In looking at this, thinking about the breakthrough residues, so this is residue that goes through your clothes, through the whole body dosimeter, into the skin, right? So the concentrations are going to likely be very small? Do we have a probability of even being able to measure that? So the uncertainty in that value measured is going to be quite high anyway, right?

DR. BARR: Right, if you, the smaller, obviously the smaller the number the more uncertainty

in the measurement of the value. So I mean it's, I mean I think that what we've all talked about and discussed is that there may be some breakthrough that may or may not be significant. There may be some amount of residue that's not able to be dislodged from the skin, but overall it doesn't seem like it's going to be a significant enough amount to put the cost and effort into correcting for it. Unless there's some simple solution that's fairly easy and not very costly.

DR. PORTIER: Okay, that's what I thought I was hearing but I wanted something nice and straightforward like that so I could understand.

DR. HINES: This is a case where you'd like all your breakthroughs to come back non-detect, this is when it's good.

DR. PORTIER: And then I, and I guess it's a similar kind of thing for the AHED protocols that use the gloves. You really don't expect a lot of the hands so you're going to have low detection levels, a lot of non-detects and a lot of uncertainty and maybe not a lot of contribution to the overall dose.

DR. BARR: Correct. It's certainly not worth the effort and cost if you're not going to have a big contribution.

DR. PORTIER: Additional questions,

comments? Cynthia.

DR. HINES: I would like to reinforce what Brian said about you may want to look at a reentry situation, reentry workers differently because of the lack of gloves.

DR. PORTIER: Jeff Evans.

MR. EVANS: Again we thank you for that and we appreciate the distinction in the types of scenarios. We didn't expect that there would be as much of an issue with this handler database. But for reentry and residential where we don't assume the use of gloves I think that's important for us to continue to think about and I look forward to any additional thoughts you have as you take these, today's events into further consideration this evening. So thank you very much for that.

DR. PORTIER: I've made a note that Cynthia has the right to

MR. EVANS: Yeah.

DR. PORTIER: come back tomorrow and revisit this.

MR. EVANS: That's been promised.

DR. PORTIER: It's really important to the discussion so we're not quite closing this issue but I think we've had a very

MR. EVANS: We appreciate that.

DR. PORTIER: good discussion on it. I think at this point we'll move on to the third charge question on passive dosimetry and biomonitoring. That should be a lot of fun.

MR. DAWSON: EPA believes that a comparison of exposure estimates derived from data collected through biomonitoring with data collected through passive dosimetry is the most appropriate way to assess the predictive nature of a passive dosimetry based approach for estimating worker exposure.

Please comment on the strengths and limitations of this kind of comparison for judging the potential utility of passive dosimetry data in conducting exposure assessments.

EPA has conducted such a comparison using available data and believes that the comparison shows sufficient concordance of estimates based on biomonitoring data and passive dosimetry data, to support the conclusion that a passive dosimetry based approach can generate data that can be used to develop relatively predictive estimates of worker exposure for a wide variety of scenarios and activities.

Please comment on the adequacy of the analysis to support EPA's conclusion.

DR. PORTIER: Doctor Popendorf.

DR. POPENDORF: Well I think overall there is, what I've been sort of setting the stage for here in looking at some of these issues of variabilities is that there are limitations to both methods. There are variable factors that cause both methods to have, to be variable in terms of the number that's being derived as an indicator of the final result that you're trying to achieve.

I think maybe a good way to view this might be the third slide on that overhead, looking at the 5 figure version, there you go. What I've tried to do with this figure is to give you a got back up two to give you a few scenarios here, looking at what we're really talking about in a pictorial sense. And on the left we're talking about the way a patch dosimeter might work and I've sort of alluded to in the previous question, the outcome of that.

What I've tried to present here is three options if you will of how to, three methods may be a good way to view it. The patch dosimeter is on the left, the whole body dosimeter is in the middle and no dosimeters basically relying on a skin wash as a passive dosimetry type method. At the bottom you'll see urinary excretion as a biomonitoring. You can do

that, potentially do that in any of these options but of course you'll end up with some errors under certain scenarios.

So let's go through that first one. The idea of a patch dosimeter, the first arrow is the total deposition onto the skin, so 100% of whatever it is. Okay, if you have patch dosimeters as I mentioned they only cover in general a small fraction, less than 5% of the skin, except for the hands where it usually would be a whole, a whole coverage. But you could use a patch dosimeter without really changing what goes to the skin. The downside of the patch dosimeter is the fact that you're estimating a dose by taking those patches, analyzing them and scaling back up to what that dose was. And that's where you get into that scaling error. And any uncertainty or variability in deposition causes that value to be quite large.

One of the questions that came is part of question 3 having to do with the concurrency if you will of dermal, or passive dosimetry in biomonitoring. If you were to use patch dosimetry that works pretty well. As you can see, the dose that reaches the skin is not changed very much, reduced only a small fraction by the portion of the body that was covered by the dosimeters which, with the exception of the hands and

how important that particular dose, is a small fraction. So it goes onto the skin, retains air, is absorbed, passes through whatever the target organs are. Some of that is going to be excreted. And I've sort of tried to indicate in that diagram that you're going to get only a fraction of the dose being absorbed through the skin so that arrow is smaller. If you tried to do something from let's blood or tissue you're going to have a scaling effect and by the time you get down to excretion you're having even a smaller fraction, trying to use biomonitoring you'll only have a small fraction analyze so you're going to have a problem of scaling back up.

The second scenario is the whole body dosimeter. There you're essentially covering most all of the body except generally the head and neck with a dosimeter which is going to get you a much more reduced dose going to the skin. Again, the same reduction, whatever that was, being absorbed in a further reduction to excretion. But if you're talking about using whole body dosimetry and concurrent biomonitoring, which is one of the recommendations on I think page 61 or so in the review, you really are, or you can't effectively do that without making some big assumptions in terms of what fraction of the whole, the

breakthrough if the dosimeter is up against the skin or if the dosimeter is not against the skin, perhaps some sort of penetration or whatever name you want to put on the amount of chemical that would go through that dosimeter which would cause the dosimeter to be slightly inaccurate, but would provide some amount of dose going to the skin, some amount coming out the, you know, with the urine. But you're looking at some interactions there that makes whole body dosimetry and biomonitoring in conflict with each other. And we wouldn't make a recommendation to try to do both.

And then the third scenario was basically the wash as a passive dosimetry type of approach. And there we talked about that earlier of how the, you don't have a dosimeter so whatever is happening at least this would apply to the hands or potentially to the face and neck. The chemical would go to the skin. At some point you'd try to wash that off but you're only going to get a fraction of that off. So there you're introducing again some errors in what you're getting off. Some is going to be retained, eventually going through. A lot of errors introduced with that method. So I think the idea of concurrent biomonitoring and passive dosimetry is not, I certainly would not recommend doing both of those. It's an

either/or sort of approach.

The previous question, I answered the issue, or tried to answer the issue of the variability of patches and what happens there. What I've presented on the next slide basically is the plot that was looking at the urinary metabolites. Now, if you just go back one we'll come up to that last one. Again, looking at no, number 4 there you are, okay.

The issue of trying to get, back calculate to dose if that's in fact the point of the database, is all going to be based on, particularly dermal dose or whatever might that be is, whatever contribution and the respiratory dose might be, back calculate on the basis of urinary excretion and what fraction of the original dermal dose gets excreted. And that's going to be the product of what's absorbed through the skin and what fraction comes out in the urine.

And those numbers by themselves are going to, most of the values that were presented in the slides earlier this morning are small fractions on the order of a percent or less than a percent of, two, maybe three-tenths of a percent. So I just took this scale down to 1, if you're actually, in some of the examples that were presented those numbers are actually less than 1% of the dose on the skin is coming back in terms

of the excretion. Well, how comfortable are you, how variable is that absorption and metabolism and excretion? I think it's probably more variable but I just kept these original 15%, 25%, 33% numbers that we had for the dosimetry.

Those were your three grades, A, B and C grades, recovery type values. And I think metabolism may be even, okay, I don't know, I'm not expert toxicologist, but I don't think you'd get down to 15%, 25%, 33% are probably more realistic numbers. And if you're looking any sort of variability in absorption and metabolism, when you're trying to back calculate a dose from an excretion in the 1% range you're looking at some very large uncertainty figures, which I think is one of the contributors to that variability in looking at the correlations that we saw earlier between biomonitoring and dosimetry.

And dosimetry has its own uncertainties but that's a major problem that I think needs to be again incorporated as part of that grading kind of concept. I think it's very realistic to put, you know, grading to metabolism studies as well as passive dosimetry.

Just as a, so it doesn't look too discouraging we'll touch on the issue of sample size, but the next slide, you know, you've got all these

numbers up here, very large individual variabilities, but if you put 16 people on, the standard error, the mean goes down with the square root of m, so I just threw on the black line there. There standard error the mean, you know, you're looking at still a few factors, less than an order of magnitude but that's why your sample size is very important. And that's taking the 25% individual variability down to the result of looking at 16 people and you reduce your uncertainty by a large magnitude. So when we talk about sample size you'll see how important that is.

I think I mentioned the issue of biomonitoring, the concurrent biomonitoring that was on page 61, that we don't recommend for a large number of reasons, including that up here. And then my only other point is the, on the issue of creatinine and correcting biomonitoring, probably not terribly important if you're fairly sure that you're getting 24 hour samples being collected. The only times it would be important is if you're going a grab sample and you don't know what the time base is. Creatinine is a good indicator of the duration that that person's been storing up and if you're trying to do 24 hour, or continuous monitoring and you want to have some quality assurance that you're getting all the urine being

produced, that is a quality assurance parameter that would add quality to the data.

DR. PORTIER: Doctor Barr, do you concur?

DR. BARR: Actually I have just a few concise comments. I think that because there's no gold standard method for assessing exposure, that the, using both methods and trying to compare both methods was the best way of ensuring that passive dosimetry does indeed meet the requirements for your exposure assessment. I think the agreement that you saw and you both demonstrated, both the task force and EPA has demonstrated is astonishing. And so either they're both right, in which case you're in a good situation or they're both wrong in which case I wouldn't know what to do.

DR. PORTIER: Brian Curwin.

DR. CURWIN: Just to maybe address the charge question a bit more specifically, there was a question about the strengths and limitations of this approach. And I think one of the strengths of this approach is if you consider the exposure dose response paradigm, biological monitoring is closer to the response and of that paradigm. And so intuitively you would think you have exposure so the chemical would get on clothing, a certain amount of that would penetrate

clothing and get on the skin, a certain amount of that penetrates into the body and you have an absorbed dose and that goes to the tissues and you have your affect.

And so if you think of that paradigm then the biomonitoring is certainly closer to that end that we're interested in which is the affect and which lends a bit a strength to it and you intuitively would think that the biomonitoring would be, would predict the passive dosimetry.

One of the limitations though is just the inherent variability in this type of work, whether it's passive dosimetry or biological monitoring, there's generally a large inter and intra-person variability. And in some cases, for example, especially where the intra-person variability is substantially larger than the inter-person variability, what you're going to have is an attenuation of the association that you're trying to see and you generally may not be able to find these sorts of associations unless you have a very good power for your studies.

In the case of what we saw here today then we've got these very good concordance, some good correlations that were significant. So if that's the case, despite this variability we're seeing, we're able to see these correlations and that, you know, as Dana

mentioned, I think that's astonishing.

In the literature generally you don't get a very good comparison between some sort of dermal exposure versus a urinary output. Usually these studies are comparing a dermal deposition value such as micrograms per centimeter squared compared to just a straight urinary concentration such as micrograms per liter or micrograms per gram.

It is possible that in the way that it was looked at by the Agency and by the task force, that by comparing calculated doses maybe we're better able to look at these, at the predictive nature of the passive dosimetry. Or it could be that the oversimplification of what we're doing here, which is, you know, is necessary in order to do these sorts of things is maybe leading to what we see.

I also am curious about some f the data. It seems that it's a bit limited. I don't have the exact numbers of what, or the data points in the task force analysis. There was 14 studies, I don't know how many data points in each study so I'm not sure of the power, but I'm curious about how the impact of some of this data may impact on what we saw. There's, if there's some repeated samples in these studies there are certainly going to be some auto-correlation and that

may impact on some of this and again the variability in the data.

DR. PORTIER: I think we're looking at one of the graphics, you can get a feeling for at least how many individual MUs that were involved in the 14 studies, just counting all the dots and it's a lot. So I have a feeling the statistical power for this was probably pretty good.

I have some other issues I'll bring up after we do the panel.

Doctor Lu.

DR. LU: I actually, I'm not surprised to see the data between passive dosimetry and biomonitoring agreeing with each other based on the presentations from the EPA and the task force group, because after all, these two methods are designed to assess exposure. From time to time there are scenario cases that this agreement will exist. And it's probably mainly because the insufficiency of passive dosimetry data.

For example, if a worker wears whole body dosimeters and there was an accidental spill on the cotton shirt, what happens is that the amount of the breakthrough deposited on the skin will not be picked up by the dosimeter. But the biomonitoring data will

reflect such addition and that's where the disagreement exists.

However according to the data presented by both groups, this discrepancy is not common so that's the good news. And therefore the predictive ability of dosimetry data for occupational pesticide exposure is recognized here. But we should stop here, we should not further use the data in terms of risk assessment and risk management. According to Doctor Baugher, I think the last presenter, he basically suggests that dosimetry data can be used much better than other data in terms of risk assessment and risk management, which I totally disagree because the way that both the Agency and the task group people calculate a dose is totally not biologically relevant.

Because the only thing that you're taking into account is the absorption on the face, there is no consideration of the distribution of the pesticide in the human body, there is no consideration of the metabolism and excretions. And there's no consideration of the time. Those are very important in terms of the pharmacokinetics, how to describe the behavior of the pesticide in human bodies.

So the solution actually is right here in front of everybody. I remember in 2005 there was an

SAP that discussed how to interpret the cumulative risk assessment using some sort of pharmacokinetic approach. And I think the Office of Research Development actually presented their accomplishments on using pharmacokinetics to calculate a dose. And what happened is that this is, to me this is a validated approach, that you have a dose estimate based on dermal exposures and you have a bunch of urine data that you collect on the same workers, what happens is you should calculate, you should use those urinary metabolite data and use the simplified PK model to calculate the drug dose and see whether this dose would match to this one. If yes, then this question will be answered in a way that, yes, that's the case.

But you are not using the same approach so you avoid a big grave box which you justify that there's no knowledge, there is no tool. Well, in the case for chlorpyrifos that's not true because the ORD model actually used substantial chlorpyrifos data to come out with the simplified PK model. And I think that EPA and the task force people should go back and use the data and use the model and pick the data that you think is most reasonable for this practice and see how much easier it is using the model versus using this simple calculation to reach the conclusion.

I think it's too, I think it's premature to reach the conclusion that these two things are the same thing. It may be the same thing for exposure assessment purposes but not for the risk assessment.

DR. PORTIER: Doctor Robson.

DR. ROBSON: It's terrible to be last so I just want to reinforce a couple things. Unlike my colleague, Doctor Lu, I actually was surprised to see the concordance and I think as Doctor Barr mentioned, many of us, before we got the packet and to be candid, most of us, until we saw Doctor Ross' presentation, because it was in the packet, but when it was up on the screen it was fairly remarkable but I think it's our feeling that it would be helpful to see the other 20 chemicals added in.

As it was brought out today there were 14 presented but there were 20 that were selected not to be in.. It would be good to see those in to look at the correlation with the benefit of the additional data points. As several people have already said and Doctor Fenske said in his comment, his written comments, a chemical by chemical analysis of concordance would really be informative for us.

One of the things that also was mentioned a couple of times is the concern, there's still a concern

about under representing the estimate of exposure.

And finally I was thinking about as we were listening to the presentation today, Jeff's presentation from Tuesday morning when you had the open mixing of the dry flowable and those three data points that were off the line and I think we have to be very mindful that whichever approach we take there are still going to be, as I think you mentioned, Doctor Portier, that could either have been glove failure or just three very unique events. But for all of us who have done this, whichever method we take we still have to be mindful that there are going to be those kinds of events. Cynthia has mentioned, you know, the example with gloves I think that we can't overlook the fact that whichever path we take or if we take parallel paths that the real field activities are going to drive this in the end.

So I don't have anything profound to add, everybody has beaten me to it. But it's okay.

DR. PORTIER: I doubt if you're going to be the last commenter on this because I want to comment on something Doctor Lu said. I was thinking back to that 2005 discussion on the back calculating through the PK model and I think the conclusion we came up with was that it's feasible but the uncertainties as you go

back through these nonlinear models just, they add up so quickly that the value you get has hardly any real, the particular measurement for applied dose, whatever you called it, is, there's so much uncertainty with it that it's almost a useful, a useless number unless you really, really know the pharmacokinetics cold, and you've been able to measure what's going on with enough frequency to be able to understand what the clearance, you know, what the clearance kinetics or if I remember correctly.

So I have some real problems with working back that way but, and before you challenge me on this, I want to say, you know, statisticians, when they see someone say, we had 36 studies and we only analyzed 14 and here they are and isn't it beautiful? The hair on the back of our head goes up, you know, because we really want to see all of the data. And so I too have some concerns that the beauty of the relationship is the beauty of the selection. You know, and I understand that the selection was done from a quality, a quality of data point of view, but that may only have enhanced the relationship. As was mentioned, you know, if you did a good study we would expect them to relate so it may be that these are the good studies and they relate. But in reality they may never really relate as

good as that.

DR. LU: Well I do not mean to challenge you but I guess I remember this because I am personally involved in this work right now.

Yes, there are a lot of uncertainties, especially you don't have that much information in the front end of the model. So that's why, if you started from the back end and the front end is empty then you kind of run into trouble. And that's why the EPA, they use chlorpyrifos as a model compound because comparing to other pesticides that are being used right now, chlorpyrifos has the most abundant data, both exposure data, human data and animal data.

In that SAP they were dealing with residential exposures so they don't really know what was the original dose was. And all they have is the biomarker data so that's how they do the backward calculaton.

As I mentioned earlier this afternoon, the occupational setting is the perfect, is the ideal work to study bio to use the biomonitoring data because we can use the estimate, the dermal estimated number as the input dose and set that as some sort of a comparison number and use this backward calculation to see what is the, a model output would be comparing to

this number. Again, you have to accept the fact that by doing this calculation, the number that we have can be considered as a gold standard because it takes into account biological and pharmacokinetic considerations. But that's kind of how I reach to my comment. No challenge.

DR. PORTIER: And I'm just thinking, you know, you have the dosimeter dose, right, measured dose and you're going to back calculate and the numbers themselves may be close but the uncertainty is going to be so big you could drive a truck through it. And so what will the, what will that really tell us? I'm not sure that's going to be there. But I think Dallas was next.

DR. JOHNSON: Yeah, I, everybody has been commenting about that figure so I guess I want to comment about it too.

I wasn't so surprised that the correlation was as high as it appeared to be in that figure, what I was surprised about was the slope was equal to 1, which does say that they're both, I can see why they might be correlated but the back transformations that were done were remarkable to make the slope come out to be equal to 1 which it apparently did.

The second comment has to do with, it seems

to me that, let me get away from any comments with respect to reality so that I don't embarrass anybody or make anybody mad. But suppose that we have a variable x and it's highly correlated with z and we have a variable y and it's also highly correlated with z, well then obviously x and y are going to be highly correlated with one another. And so it seems to me that in what we're looking in this case, z is some of risk that we actually haven't even measured yet. But we believe that these amounts of residue that get inside the body have some affect on risk. And so what, how they correlate with risk probably doesn't matter too much with how we measure it, whether we measure it through dosimetry or we measure it through bio measuring urine. And so either one of those would be correlated well and from a statistician's point of view I'm completely happy to use either one.

DR. PORTIER: Doctor Chambers.

DR. CHAMBERS: I think I'm going to argue with my friend Alex Lu also. In a lot of the points that have been brought up about the physiology are very important to consider and it actually kind of came up at lunch a little bit too, is that people vary a whole lot in their size, their physiology, the metabolism is going to vary with sex, age, what have

you, you know, physical condition, body fat and storage of lipophilic compounds and all.

So it really seems to me in thinking about this that when you get down to the biomonitoring and what's coming out in the urine, that's going to be driven an awful lot by the individual that you happen to choose to monitor at that particular point.

And conceptually if I understand what this whole process is about it's about developing a generic database that can be used across a variety of different occupational settings and a variety of different compounds that would be widely applicable.

And Alex, all the stuff he was talking about is very well taken I think if you're talking about a particular compound. And if you wanted to do an assessment on chlorpyrifos in particular, back calculating that from the well known pharmacokinetics would be useful. But in trying to develop a generic database here it seems like what is going to be the most accurate thing is what is deposited on the body, the passive dosimeters that can be used generically across again all the different occupational scenarios and across all the different compounds. And it's not going to be driven by the efficiency of one compound being metabolized very, very effectively compared to

another that is not.

So I would, my opinion in all of this is that the efforts are best spent in trying to develop the very best passive dosimeters possible that would be most applicable to the generic database and to de-emphasize the biomonitoring that is going be biased or influenced maybe not biased but influenced so much by the individual compound and the individual's physiology.

DR. PORTIER: Doctor Handwerger.

DR. HANDWERGER: Excuse me, I'd like to certainly support those comments because I've been looking at urine values for diagnostic purposes for 40 years and I can tell you I really believe them, because yes, you may stand there and monitor people in the field and you may make sure they go to the bathroom and you've got the sample, but they are not spending 24 hours under your observation. And it's very hard to get 24 hour reliable urines. I can't even get it done in a hospital or being supervised on a clinical research unit unless I have special nurses who understand that you begin the 24 hour collection on an empty bladder and you end it by urinating at a specific time so you get a true 24.

It sounds very simple but I can tell you it's

very hard to do and I think you're going to underestimate the reality of the situation because you're not going to get 24 hour urines.

Secondly, if you take anyone in this room and have them collect their urine every day for 24 hours and do it absolutely perfect, there will be a very striking differences in the creatinines over that period of a week. It won't be 1,000 plus or minus 53, it'll be 1,000 plus or minus 400. There is wide variation in daily creatinine.

So I don't, I can't look at a creatinine and say, aw, this is really representative of what is a 24 hour urine for that person. I can't do that, I can tell you whether it's really a 2 hour collection but I can't tell you that it's a 24 hour collection. So I'm very suspicious when it comes to evaluating urinary data unless I know how it's being done and who is collecting it.

I review these papers for endocrine journals, collecting 24 hour urines as part of a study and boy, we really want to know exactly the experimental conditions under which it was obtained. And I think you'll underestimate your values and I think rather than trying to deal with almost an impossible situation to get really reliable numbers, I think your exposure

data is going to be a lot simpler and much more efficient in doing that.

DR. PORTIER: Doctor Curwin.

DR. CURWIN: Just to echo Doctor Chambers and Doctor Johnson, I think the ultimate goal here for the Agency is to do a reliable risk assessment on these chemicals. And so if we have a very accurate passive dosimetry method and then can compare that to toxicity studies that are dermal exposure as well I think we're going to have a better estimate of a risk in that sense.

And if we can compare what's deposited on the skin in the workers versus what's deposited on the skin in our health effects studies, I think that's going to be certainly more reliable and that's what I think Doctor Johnson was getting at, that we're not really, that we haven't really put this in the context of the health effects and the risk assessment.

DR. PORTIER: Doctor Lu.

DR. LU: I may sound like I'm running some office but I'm not. Let me, the limitation about biomonitoring or urinary metabolite is well taken. And actually things are changing right now in the field. For example the simplified PK model, the minimum criteria for the data to be able to use in the

simplified PK model is two consecutive urine voids. That's because that we need to know the time of the void and use the volume to back calculate. A 24 hour total void sample would be ideal and perfect but it's not going to be the case for everybody. And that's why, or to actually test the two consecutive urine model and they use this to compare to the data that comes with the 24 hour total void. And they found that it's really not that much different. They also test a different scenario but it's, most of it is not related to occupational settings so I don't want to bring this up.

In terms of individual variation and between a person's variation, yes, there are definitely the case, but if you look at, I don't want to say well designed studies, but if you at studies that's designed specifically to answer those questions and if you look at the variation that's coming from the biological data versus the variation coming from say for example, food consumption, they are approximately in the same ballpark number, the range.

So I mean you talk about one thing or the other you have to think about, if you think the variation associated with the biological data is too large to be acceptable, then you have to think about

what is the counterpart and what is the variation. In this case I will argue that if you look at the hand, the dermal exposure, the handwash or the skin wipe, they are as variable as biological data. There is no perfedt solution for this.

DR. PORTIER: Doctor Chambers.

DR. CHAMBERS: But I think part of the variability in the urine is going to result from the differences in the physiology of people. The variability in the hand washes and everything is kind of inherent I believe in the technique itself. So it seems like if you're going down, you've got variability in the occupational exposures but what people do and how much they get deposited on themselves, if you go to the level of biomonitoring you've introduced even more variability. And it just seems like from the standpoint of a generic, to me, form the standpoint of a generic database for exposure that keeping it up at the level of what the occupation is creating is going to give better data that will be more generally applicable.

DR. PORTIER: Doctor Kim and then Doctor Handwerger.

DR. KIM: Yeah, just a comment about variability. It's my understanding that variability

and uncertainty have to be really well distinguished. Variability is a good thing for risk assessment. You want to capture that variability and you want to incorporate that, those sources of variability in any risk assessment because you want to capture as much of the population as possible.

The other thing is, there is a direction toward more refined risk assessment by looking at tissue dosimetry, understanding what the target tissue dose is and linking that with the toxicological data, adverse health effect, et cetera. And the only way I see that that can be done is to use a pharmacokinetic model. And in order to develop a pharmacokinetic model it takes a lot of time, you need, you start with an animal study, you can do a controlled human exposure study but you definitely also want to go out into the field and validate that model against human exposure data. And much of it comes from urine, urine biomonitoring data or blood biomonitoring data.

DR. PORTIER: Doctor Handweger.

DR. HANDWERGER: Just a very minor point to Doctor Lu's comment about collecting a sequential couple of urines. Of course things are not released into the urine at a linear rate. A compound like a

pesticide metabolite may be very rapidly excreted so that 90% of it is urinated in the first hour or two after the initial exposure to the material. So I don't think that if you're going to do it you're going to have to do it looking at a long time interval so that you'll be sure that you're getting all of it. And I don't think that just collecting a couple of spot urines will necessarily provide you with the information for all compounds.

DR. PORTIER: Dallas.

DR. JOHNSON: A comment, a lot of the studies at Kansas State that involved animals where they want to look at, and they're going to measure urine because they can put their cows and calves or whatever sheep in cages, they often would not give them water for 24 hours prior to starting to collect data and then give the chemical or injection and then let them have water so that you sort of, you sort of put everybody on a similar standard beforehand. But I think you can take your workers and keep them from having water for 24 hours prior to collecting data.

DR. PORTIER: I'm sure that wouldn't go over well with the Human Studies Review Board. Doctor Appleton.

DR. APPLETON: Yeah, the Forest Service

can only offer one more data set. But about five or six years ago we commissioned a dermal exposure biomonitoring study for 24D which has a lot of good things going for it, it's been beaten to death with study for three generations and it's amenable to biomonitoring.

Our contractor in Syracuse who, Jeff Evans I think mentioned his name this morning, Pat Durken, massage the data in the literature from industry in support of the re-registration and compared that with our biomonitoring data and developed actually a PBPK model from it. And I'll tell you the data matched like that. It was really, really close. It could be an exception but this is one more vote for the biomonitoring people over here.

DR. PORTIER: I think we've, oh, one more comment, Doctor Barr.

DR. BARR: I have to have the last word on biomonitoring. I think it is going to be compound specific. I mean some pesticides are metabolized to multiple metabolites. The metabolism is very variable among people. Some pesticides are very consistently, like 24D, very consistently excreted as 24D. Those are much easier to deal with and so I think that you're going to find a wide degree of variability among

pesticides. And so if you're trying to, sorry Alex, is you're trying to make a generalizable or a general database I think that using biomonitoring data would not be the best place to start.

DR. PORTIER: Alex.

DR. LU: Yeah, well in the

DR. BARR: You won't let me have the last word.

DR. LU: I need to have the vote.

DR. PORTIER: I have the last word.

DR. LU: Well again I emphasize that one of the components in using the pharmacokinetic model or in all those estimate calculations, is that you need to know the time. I'm not saying you can just go out and take any consecutive urine sample and then forget about the rest of the information. No, that's not the case. I remember I said so. You need to know the time of the void. The reason that you need to know the time of the void is because, up, here is a hypothetical question. You spray chlorpyrifos and the application ends at 1:00 p.m.

You have two consecutive urine samples, one at 7:00 p.m., one at 9:30 p.m., okay? You put those information into a simplified PK model. The billion other reasons would know that between the void, the

concentration of the chlorpyrifos in the urine within the absorption phase, the first decay phase or the second decay phase, assuming there's a two compartment distribution.

And from there the model will calculate the rest of the stuff that you want. If you don't input the time the model will not move on to the next window. So that's the key for set up, you have to know time. And my criticism, if that's truly a criticism to the Agency and the task force is that when you do the absorbed dose you ignore the time. And that's very critical. Even though you take an average it doesn't really mean anything.

DR. PORTIER: Doctor Popendorf. I'm getting the feeling that when you write up this report you're going to have a minority, a little bit of a minority opinion that's going to need to be represented in here.

DR. POPENDORF: It sounds like it to me as well. I've heard a couple of, you know, there are certainly a couple of argue approaches that are being proposed to this and I think to just kind of remind you, the issue that I'm talking about and a couple other people and several people have mentioned, sensitivity analysis. And I think, you know, to the

Agency that is certainly something that you guys can also pursue in terms of look using some sensitivity analyses on what you do, the issue of how variable the model is, you know, you, again you might get exactly the same result, but if you look at the uncertainties that go into the calculation, the confidence that, it's called propagation of errors, another kind of theory to that, and the uncertainty in the range of the results could very well be comparable to some of the analyses that I have generated here for the dosimetry side.

They're relatively easy to do because there's fewer parameters but the same approach could be taken to the model to generalize in terms of, well, how certain do those parameters need to be? And I think that could give you guys a lot of, you know, you've got the accuracy and the precision issues. And they sometimes interact but they are different and if you're looking for confidence or trying to interpret these other questions that are going to come up in terms of like linearity, can you really discern linearity from issues of variability in the data because of modeling or passive dosimetry or the biomonitoring or whatever approach that you're using? They all have variability built in. You just need to keep that in mind and try to quantify it. I think it gives you a real sense of

reality.

DR. PORTIER: I think we've pretty much discussed this. It's going to be interesting to see what comes out on the report on this one.

We actually may revisit this again tomorrow because tomorrow's discussion is going to center around variability and uncertainty and relationships in terms of the proportional stuff. So we may come back to some of this.

But I think we're ready to kind of draw a close to this discussion unless I see a dissenting remark. I don't see any.

Does this look like you got the, a feel for how the panel is going to fall out on this?

MR. EVANS: We do indeed, we sense a building momentum of additional thoughts in this matter, especially as we get into some of the other presentations we'll see in the next two days. And again we thank the panel for a very thoughtful discussion.

DR. PORTIER: Good. At this time I think we're going to call the meeting to a close for today. Because of the way we've structured the discussions and the questions for this particular SAP, there's not a big opportunity for us to move ahead very quick with

the program. For example we really don't want to go on to the question 4 until we've had the discussion tomorrow morning.

So I think at this point we're going to stop. The panel is going to meet again at 8:30 tomorrow morning, same time, same place.

Myrta, do you have any closing comments?

MS. CHRISTIAN: None at the moment, no.

DR. PORTIER: No. So I think we'll call it closed at this time. Thank you.

(WHEREUPON, the meeting was adjourned at 4:21 p.m.)

CAPTION

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

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

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

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COMMONWEALTH OF VIRGINIA

AT LARGE:

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

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

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

MARK REIF, COURT REPORTER / NOTARY

SUBMITTED ON JANUARY 10, 2007

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