U.S. ENVIRONMENTAL PROTECTION AGENCY

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FEDERAL INSECTICIDE, FUNGICIDE AND

RODENTICIDE ACT SCIENTIFIC ADVISORY PANEL
(FIFRA SAP)

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OPEN MEETING TO CONSIDER AND REVIEW DRAFT FRAMEWORK AND CASE STUDIES ON ATRAZINE,

HUMAN INCIDENTS, AND THE AGRICULTURAL HEALTH STUDY: INCORPORATION OF EPIDEMIOLOGY AND HUMAN INCIDENT DATA INTO HUMAN HEALTH RISK ASSESSMENT

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The Panel convened at 8:30 a.m. in the Lobby Level Conference Center of the U.S. Environmental Protection Agency, located at One Potomac Yard, 2777 Crystal Drive, Arlington, Virginia, Steven G. Heeringa, Ph.D., Chair, presiding.

FIFRA SAP CHAIR PRESENT:

STEVEN G. HEERINGA, Ph.D.

DESIGNATED FEDERAL OFFICIAL PRESENT:

MYRTA R. CHRISTIAN, M.S.

FIFRA SAP MEMBERS PRESENT:

JOHN R. BUCHER, Ph.D., DABT
JANICE E. CHAMBERS, Ph.D., DABT, A.T.S.

GERALD A. LeBLANC, Ph.D.
CAREY N. POPE, Ph.D.
KENNETH M. PORTIER, Ph.D.

FQPA SCIENCE REVIEW BOARD MEMBERS PRESENT:

JOHN C. BAILAR, III, M.D., Ph.D.

FRANK J. BOVE, Sc.D.

RICHARD GREENWOOD, Ph.D.

ELLEN B. GOLD, Ph.D.

SHELLEY A. HARRIS, Ph.D.

WILLIAM L. HAYTON, Ph.D.

CHENSHENG LU, Ph.D.

BETTE MEEK, Ph.D.

NU-MAY RUBY REED, Ph.D., DABT

JOHN S. REIF, D.V.M., M.Sc.

T A B L E O F C O N T E N T S

P-R-O-C-E-E-D-I-N-G-S

8:37 a.m.

MS. CHRISTIAN: Good morning. I am Myrta Christian, the Designated Federal Official for this EPA meeting.

I would like to welcome everyone and to thank you for participating in the last day of this meeting to review the Draft Framework and Case Studies on Atrazine, Human Incidents and the Agricultural Health Study: Incorporation of Epidemiology and Human Incident Data Into Human Health Risk Assessment.

Without further delay, I would like to introduce Dr. Steve Heeringa, Chair of the FIFRA SAP.

CHAIR HEERINGA: Good morning everybody and welcome back to what will be the final day of our three-day meeting of the FIFRA Science Advisory Panel on the topic of a Draft Framework and Case Studies on Atrazine, Human Incidents and the Agricultural

Health Study: Incorporation of Epidemiology and Human Incident Data Into Human Health Risk Assessment.

At this point, we would normally do introductions and I think we'll do that quickly this morning just to make sure we get this covered.

I'm Steve Heeringa of the University of Michigan. I'm a member of the permanent FIFRA Science Advisory Panel.

MEMBER PORTIER: Good morning. I'm Ken Portier, Director of Statistics at the American Cancer Society. I'm a biostatistician and a member of the permanent panel.

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

MEMBER BUCHER: John Bucher, Associate Director, National Toxicology

Program, NIEHS.

MEMBER POPE: I'm Carey Pope, Professor of Toxicology, Oklahoma State University.

MEMBER MEEK: And I'm Bette Meek, Associate Director of Chemical Risk Assessment at the University of Ottawa, McLaughlin Center, on interchange from Health Canada.

MEMBER GREENWOOD: I'm Richard Greenwood. I'm a Professor of Environmental Science at the University of Portsmouth in the United Kingdom.

MEMBER HARRIS: Hi, I'm Shelley Harris. I'm Associate Professor at University of Toronto and a Scientist at Cancer Care Ontario.

MEMBER BOVE: Frank Bove, Senior Epidemiologist, Agency for Toxic Substances and Disease Registry. It's part of CDC.

MEMBER LU: Good morning, Alex Lu from Harvard School of Public Health. I do pesticide exploration and research.

MEMBER GOLD: Hello. I'm Ellen Gold, Professor and Chair of the Department of Public Health Sciences at UC Davis and Chief of the Division of Epidemiology.

DR. HAYTON: I'm William Hayton, Professor of Pharmacy, Ohio State University.

MEMBER REED: Nu-may Ruby Reed, Toxicologist, California Environmental Protection Agency.

MEMBER REIF: John Reif, Professor of Epidemiology, Department of Environmental and Radiological Health Sciences, Colorado State University.

MEMBER LeBLANC: Gerry LeBlanc, Professor and Head of Department of Environmental and Molecular Toxicology, North Carolina State University.

CHAIR HEERINGA: Thank you very much, members of the panel. And I think Dr. Bailar will probably join us. Here he is.

Before we turn to the continuation of our discussion of the charge questions,

I'll just turn to Dr. Lowit to see if there is any follow up from the proceedings from yesterday.

DR. LOWIT: No, there's not.

CHAIR HEERINGA: Okay.

DR. LOWIT: But we really enjoyed yesterday's conversation and we look forward to the next couple of hours.

CHAIR HEERINGA: Thank you, thank you.

Okay. Without further ado, then, let's read -- we've completed our initial discussion of charge questions one through three. And again, for panel members, before we conclude the session this morning, we'll give everybody a chance to sort of go back and any last thoughts that you might like to add into the process in the public record, we'll do that.

But let's turn now to Charge Question No. 4. Shalu, if you would read Charge Question 4.1.

MS. SHELAT: Good morning.

Question 4.1., The Agency believes prospective epidemiology studies with robust exposure assessment, like the AHS, have the greatest potential for use in risk assessment especially for enhancing problem formulation and risk characterization. Please comment on appropriate ways to use these types of epidemiology studies in risk assessment.

CHAIR HEERINGA: Dr. Harris is our lead discussant on this one.

Shelley?

MEMBER HARRIS: Well, good morning, everyone. And excuse my coughing and my cold. I've been fighting this all week. So I'll try to keep that down.

I thought that I would -- you know, you have the luxury of having two days of conversations and discussions and then we get the final question today. It's a luxury and sometimes a little bit of a curse.

But I thought that what I might do

is answer this question in two parts. And first look a little bit -- talk a little bit about study design issues and attempt to summarize briefly what has been discussed over the past two days and bring it into context of prospective cohort studies. And a little bit about some of my thoughts on the different uses of prospective cohort studies in the risk assessment process.

So first of all, over the last couple days, we've discussed different design features of the epidemiologic studies and methods to qualitatively and semi-quantitatively evaluate them and also discuss some of their potential limitations and how we would make most efficient use of this kind of information in the risk assessment process. And for also risk management and risk mitigation.

And when we, as epidemiologists, when we teach epidemiology, we often describe studies from their weakest to strongest. And

that's sort of the approach we've taken in these sessions I think. We would say the weakest studies may be case reports or incident reports followed by clusters. This is nothing new to most epi people in the room.

We would then talk about cross-sectional studies or ecologic studies, looking at grouped data with grouped exposure measurements, retrospective studies, case-control studies, retrospective cohorts. And then finally leading up to the prospective cohort designs that we are addressing today assuming that those are the strongest designs to answer these types of questions.

But I would say that's not always the case. It really depends on the question being asked.

And I think that the EPA has taken a similar approach in grouping these studies into three main categories: the ecologic studies, retrospective studies, and the prospective studies. And I think that's --

from what I've heard over the last two days, it is very difficult to generalize strengths and weaknesses and limitations of these types of studies.

And, again, it depends on the questions being asked and what kind of data you need to obtain. So a cross-sectional study might be absolutely perfect to biomonitoring or to look at some kind of absorbed dose estimate that you may need for the risk assessment.

One thing that I think we all discovered is that we need some additional clarification in that document, the framework document, about exactly what a retrospective study is or we need to be very clear on that terminology.

So from our perspective, a retrospective study is something you hear -- epidemiologists would say a retrospective study is a case-control study, something where you define the health outcome and you look

back and assess exposures whereas a prospective study is something where you define a group of individuals or cohort and follow them ahead in time and look at the health outcomes.

And so it is prospective in design. But we may -- where it gets confusing is we may have a historical cohort, that might be a better term to use, where you identify a group of individuals or a cohort in the past and measure their exposures over time. So that still has a prospective component.

And so I think it is important to make that distinction because a retrospective cohort can be very cost effective and efficient and answer your questions quickly if that's what you need done.

So having said and with all those disclaimers, I think ultimately we think of the prospective cohort as the best study design to answer some of our research questions associated with pesticide exposure

and health effects. And I think that's, in part, because we have the opportunity to collect the best exposure measurement or the best exposure data.

That doesn't necessarily mean we do collect the best exposure data. It's just we have the opportunity to do so. And the agriculture health study is an example of a study that really sets the bar pretty high for future studies and future cohorts on how best to go about collecting exposure information in a cost-effective way and then having it be very useful for industry, for the farmers, occupation, and also for risk assessments. So there are many, many more uses other than just risk assessment.

What I will say is as epidemiologists, and we have a really good handle on ascertaining cases and health outcomes and bias and that type of thing, but what we're never really good at or weakness in all studies, not just prospective studies, is

exposure measurement. And I think that's particularly relevant when it comes to pesticides. So if you want a particular epidemiologic study of any design, the first thing we will look at is how exposure was measured or not measured or what proxies were used and how much measurement error was associated with that.

And so I think that really needs to be our focus when we're looking at these studies and evaluating how -- qualitatively and quantitatively how good they are and how they should be weighted for risk assessment purposes.

And so which is great because that's our focus of the next question today, how do we go about using these great epidemiologic studies for risk assessment.

So I'm move on just a little bit just to the second part of the question. So I think that, you know, the prospective design is a great design is it is carried out and

conducted efficiently.

Some the advantages of using -- or having prospective cohorts such as this and others that are underway is that you can collect -- you can look at exposures and absorbed dose in the relationships between these things for single exposures and multiple exposures. And that allows us to look at these exposures over time and potential interactions and effects of mixtures, which I know everyone is interested in.

And it also helps to find what are the expected concentrations or doses that we would see in humans to feed back into the tox testing and the animal testing. So that's very helpful in an of itself.

We can look at changes in exposure over time so we're not interested in just daily estimates. We're interested in estimates of exposure over season and over a lifetime, how those vary, peaks and min/max values. And that's all very important

information to obtain.

So of that we can capture a bit on questionnaires but typically we can capture that with great biological monitoring studies or validation studies that are incorporated into those cohorts.

So I think this will come up quite a few times -- this will come up in the next few questions but I think that we really need to concentrate more effort on conducting validation studies within our cohorts and with biological markers that are well defined, biological makers of exposure and also lead into -- so I think we need to do these types of validation studies, looking at relationships between questionnaire data, absorbed dose estimates, and also exposure data and predicted exposures. And that's where that PHED database and those kinds of databases come in.

I think another advantage of the cohort studies -- prospective cohort studies

is that not only do we have the ability to look at the biological markers of exposure but the markers' susceptibility and effect. And that helps us to understand more about mode of action and mechanism. And so that's a real advantage to cohorts when well designed.

Let's see what else I have. I will, again, I have a lot of disclaimers. You know I talk about these advantages of the prospective cohort and that we can calculate absorbed dose. Well we might do that effectively for one day in a lifetime for one individual in the cohort. I mean it is impossible to calculate or measure absorbed dose of individuals over time. It's too expensive. We all know the issues with that.

So when we're talking about validation studies, you know, we say biological monitors is the gold standard but it's, you know, it's an alloyed standard in some ways. You've got to realize that this is not the true measure that we're looking at.

So that needs to be taken into consideration and good validation studies designed with repeated measurements and looking at variations within and between individuals over time I think is going to get at some of these issues.

And I think I'll leave it at that and let my colleagues jump in.

CHAIR HEERINGA: Thank you, Dr. Harris.

Dr. Greenwood?

MEMBER GREENWOOD: I think that if these studies are going to be useful, it is exceedingly important to get the stakeholders involved at a very early stage because you are going to need a lot of cooperation from these people in order to get the relevant exposure data and make sure that you can validated the exposure because that's pretty crucial when you are going to start comparing different methods of assessing exposure. You really need to have some gold standard you can

compare with.

And I think it's just going to be important to accept very large confidence intervals, very wide, because with the best in the world, there is a lot of variability between individuals in the ability to metabolize, for instance, and which metabolites are present.

One of the pitfalls I think I've seen in some of these papers is that people look at the correlation coefficient R and they get .4 and they seem pretty please with that. Well, actually r-squared is 0.16, that means only 16 percent of the variation is shared, which means that 84 percent isn't.

So, you know, but on the other hand, that's the nature of exposure data, pharmacokinetic data. And I think you're going to have to be able to work within that variability. And one of the problems that you face is just the expense of these studies, these biomonitoring studies and the difficulty

of getting people involved.

And I think it means that you're looking at something with a great deal of variability. And you're having the worst of all situations, a small sample size to try to get a fix on it. So I think you really need probably to work within the confidence intervals rather than the small sample going for measure of location.

Now having said that, I think that this is probably going to be very important if you're going to be comparing two data sets. It's one way that you can have common measurements. You've got something you can tie it down with.

Thank you.

CHAIR HEERINGA: Thank you, Dr. Greenwood.

Dr. Chambers?

MEMBER CHAMBERS: I had three thoughts while I was considering this question. One is that if the diaries on

current usage, I think are probably quite accurate in terms of services exposure. But if anybody is going to be asked about things that they were exposed to historically a large number of years ago, I think the accuracy of that is probably not as high. And I think you need to make sure you take that into account.

Certainly the Ag Health Study is very impressive in its size and its dimensions and that sort of thing. However the long-term outcomes of that are probably going to be quite a while in the future. And whether or not -- just how useful that will be for today's risk assessment is a little hard to say. But it will take a while to get the information.

The last thought I wanted to mention is that there are some more current exposure databases that will be forthcoming very soon as you well know. I sit on the Human Studies Review Board for EPA and we are in the process of -- or over the last couple

of years have been in the process of evaluating and making recommendations about the protocols for the Agricultural Handlers Exposure Task Force studies on what -- 25 scenarios, I think, of different agricultural activities. And this is designed to give more current exposure data to replace the very old PHED data that is probably not so accurate for today's agricultural practices.

So as that data is forthcoming, that should really displace any of the PHED data if it really reflects more accurate studies. So that will be better exposure data.

CHAIR HEERINGA: Thank you, Dr. Chambers.

Dr. Portier?

MEMBER PORTIER: I don't have a whole lot to add. I think the real benefit of these prospective cohort epidemiology studies, beyond their ability to follow individuals over time, is the ability to gather

information to support modeling of a lot of the lifestyle factors, work environments, and how these things change over time, over a lifetime for an individual.

And I think this is the kind of information that is going to really help complement EPA's scenario approach because one of the things that you miss in the scenario approach is knowing how often and when the individuals view these scenarios.

So when you start trying to put them together to try to come up with the lifetime exposure, cumulative exposure statistic, you are going to be kind of modeling that. And you are going to meed a lot of information to model it.

And that information is going to come from these prospective studies. Again, as Dr. Chambers said, retrospective studies have the problem of recall bias that -- and once you put that into modeling, it just kind of cumulates that issue.

Also thought about how prospective epidemiology studies can help in hazard identification. And I think it provides the kind of health effect differences for the different cultural, behavioral, dietary, health factors, information on co-morbidities, a lot of that information you are going to need and just identifying the population you are looking at. For exposure assessment, it does the same thing for exposure for a lot of all of these factors.

And then the last thing, I think, is the dose response relationship. Depending on the underlying structure of the targeted population, whether that's a very focused population like the Ag Health Study or more broader cohort studies, if they -- assuming they have validated measures of true exposure, the data from the prospective studies should provide useful information on human responses to varying levels of exposure.

And has been stated here a number

of times, that's a large need to do a really good risk assessment that links animal data to human data without using a lot of uncertainty factors and all these other things. So I think that's the real benefit.

Something Dr. Chambers said got me thinking about what one of the -- no, it was actually something Dr. Greenwood said about engaging stakeholders. The American Cancer Society, as many of you know, has a large cohort study that we've done for years. And one of the benefits of being in a not-for-profit is we can engage these people who are involved in this cohort study and may become part of our family, right? We continue to communicate them and we keep them on our side and they want to give us information.

The problem with EPA is you are a regulator and it is hard for you to engage them in that kind of relationship. But you may want to look at how you utilize other partners who have those kinds of relationships

to get the kind of cohort -- prospective cohort data that you need.

I was sitting there thinking we're -- the American Cancer Society is in the process right now of recruiting for a prospective cohort study of a million people. I think there are going to be a few farmers in that and pesticide handlers in that database. I'm going to have to go back and see if we've got any right now. We only have 60,000 in the cohort right now but -- and that kind of cohort, they're collecting blood samples at recruitment so we'll have the early-day kind of information.

And I don't think we're alone in this kind of endeavor. There are a bunch of those kinds of cohorts going on where you might be able to extract that kind of information.

I think that's all I have.

CHAIR HEERINGA: Dr. Reif?

MEMBER REIF: Three comments just

to follow up. Dr. Harris did a good job outlining the general strengths of this prospective approach. And we would all -- I think epidemiologists certainly support that, recognizing that these studies are still uncommon because they are so large and so difficult and expensive to undertake.

So one of the -- I think one of the advantages or one of the opportunities of these kinds of studies is to collect quantitative exposure data as well as evaluate biomarkers that may be intermediate steps on the pathway to disease.

And initially when you think about this, it's daunting with respect to the logistics and the expense. But the way that I think the Agricultural Health Study has considered this is to do subsets. It isn't necessary to collect blood or analyze urine for pesticide metabolites from every single person in a cohort if a reliable and well-thought-out study design for the subset

sampling can be developed.

And I know that the Agricultural Health Study has thought about this extensively since the initiation of their study but has, in some instances, I think been hampered by lack of resources to do as much as they would have liked to do.

Again, Dr. Alvanja, of course, would be the best person to comment on that but I think there are opportunities and there have been efforts made to do some evaluation of exposure using biological monitoring. And I think that should be clarified because I think that's really the key to the next kinds of steps that the Agency would like to undertake, which is to use data like this in risk characterization, not just in hazard identification.

Your problem formulations don't really need a study like this. It helps but other studies can lead one through the initial steps.

It's the risk characterization phase of this that's the trick, of course. And I know, of course, the Agency's deliberations collaboratively to work with NCI and other partners to try to figure out how to model these exposures is commendable because at the end of the day, it's developing accurate exposure measurements and measurements of intermediates that can, in fact, I believe lead to risk characterization information that can then be put into the risk assessment framework and compared side by side with animal data. And that, I think, is the ultimate goal of the use of epidemiology in risk assessment.

And it is challenging and daunting. But you are correct, that I think this kind of study gives you the maximal opportunity to do that.

I think there are some examples out there. There has been some discussion in the meeting about other attempts, perhaps with

TCE, also the arsenic literature I think is a useful place to look. EPA, of course, has been involved in standard setting or in development of MCLs from arsenic epidemiology data and much of that collected by Allan Smith and others might be relevant.

And actually there are at least one paper that I remember that Allan Smith and Berkeley wrote which actually describes the incorporation of the arsenic data into a risk assessment model. It's an older paper now. It's in the `90s, I believe. But there may be some information in that that can be useful as a model for how, in the arsenic case, one could approach risk characterizations.

So I think the risk characterization, that's the Holy Grail of this whole exercise with respect to the incorporation of epidemiology data. And Dr. Portier mentioned dose response relationships and I alluded to it yesterday to help understand for whatever outcome, the shape of

these dose response relationships in humans, that would be a very important goal, I think, of this exercise.

The last comment is that some endpoints lend themselves better to risk characterization in a cohort study like this than others. And I go back to the idea that for reproductive outcomes, given the finite and relatively short period of interest, perhaps a year from the initial exposure to the endpoint, this makes risk characterization in the Agricultural Health Study really more feasible.

If the exposure data are collected at the appropriate points in time and if they have been collected at appropriate points in time for women who become pregnant, then there is an opportunity to look at these subsets again in a very careful way. And that's why I asked the question the other day -- yesterday -- about linkage with birth records because I do believe that there are

opportunities to explore reproductive endpoints beyond what's been already done in the Agricultural Health Study for any chemical. And in this case, the interest is in atrazine. So this, I think, is an opportunity that should be explored in depth. And with, of course, the assistance of NCI, I think that perhaps some progress can be made in that area.

The resolution of the exposure assessment between the EPA methods and -- which, I guess, is the next question -- so I'll stop here.

CHAIR HEERINGA: Thank you, Dr. Reif.

Comments from other members of the panel?

Dr. Lu?

MEMBER LU: I'm Alex Lu. In my opinion, I think the Agricultural Health Study probably is the best that we can get in terms of using the data for the purpose of a future

risk assessment. I'm pleased that the Agricultural Health Study is still ongoing, you know, Phase II, Phase III studies.

But I do disagree that their exposure assessment method is robust just because they dichonomize so many exposure categories, you know, zero, three, nine, and so on and so forth. It's really easy to either magnify or, you know, significantly reduce exposure if you add those things up together.

However, I do see a great opportunity that EPA can work with the Agricultural Health Study by introducing your unique exposure concepts because this is an occupational database. It may take a while. It may require some effort. But if you were able to look at their exposure intensity information and convert it to your unit exposures metrics and see whether you can come to the same result, the outcome in terms of disease association and so on and so forth.

And as I recall, Dr. Alavanja yesterday mentioned that in Phase II, Phase III, they're going to come out with chemical-specific exposure intensity. That's even better because you can actually go in and look at not just the chemical-specific exposure data, you can actually create a matrix that nobody in the world has in terms of the same person sprayed different pesticides, what would be the health outcomes.

So I think my comment is just, you know, treat that as a data gold mine. And use your expertise. Unique exposure has been reviewed many times and the new data will come out. I think it is prudent to just limit these two datasets together.

CHAIR HEERINGA: Thank you, Dr. Lu.

Dr. Bailar?

MEMBER BAILAR: I understand that the -- from the comment the other day that the Agricultural Health Study is not recruiting

any new members. The current subjects are getting older. They will eventually diminish substantially in number. That might make room for a new kind of study.

The question that I would have is not whether the data we have now on exposure are perfect, they're not. But can we do any better if we were to take this on again? And I'm not sure about the answer to that. It looks to me like the present study is doing pretty close to the optimum as of our current knowledge. But it would be worth some thought about whether there is going to be space for another -- a similar study with a younger cohort, a new cohort. And if so, how that might be attacked.

CHAIR HEERINGA: Thank you, Dr. Bailar.

That's a key issue in any longitudinal study program.

MEMBER HARRIS: Yes, oh, sorry.

CHAIR HEERINGA: Oh, Dr. Harris,

please?

MEMBER HARRIS: Oh, can I?

CHAIR HEERINGA: You can say it.

MEMBER HARRIS: Oh, I think, you know, given sufficient funds, we can do just about anything in a cohort study and they all could be much better. So I think -- so are you asking, you know, how would we improve on this?

CHAIR HEERINGA: I'm not asking about what's possible but what's feasible.

MEMBER HARRIS: What's feasible.

CHAIR HEERINGA: You know within foreseeable budgets and limits of trained personnel and so forth, number of subjects.

MEMBER HARRIS: Well, I think if I was to initiate another cohort study such as this in an agricultural setting or an occupational setting, I would certainly try to supplement it with biological samples that were collected within individuals over time. But that's a very expensive endeavor as we

know. And so whether that's feasible or not, is another question.

CHAIR HEERINGA: Dr. Portier?

MEMBER PORTIER: That reminded me of something I was thinking of which was the idea of recruiting the younger cohort. If the Ag Health Study is anything like a lot of the cohorts I've seen, you know, the average age is in the mid to late `50s. And so you're having to do retrospectively back to when they started forming.

You know most of them left college and starting forming the family forum when they were in their mid-20s. So you've got 30 years of exposure before you get them in a prospective study, which is okay for cancer outcomes but maybe not great for reproductive outcomes.

So I think there is room not just in biomarkers and collecting blood samples but actually actively recruiting younger growers into this kind of program so you get that

lifetime. I know it's more expensive because now you've got to follow them for 60 years instead of 30 years but we'd get a lot more information on them.

Thanks, John.

CHAIR HEERINGA: Dr. Gold?

MEMBER GOLD: I was intrigued actually when Dr. Alavanja was talking about the challenges of dealing with the offspring, that they actually might think about the Framingham model which generated an offspring cohort in relationship to the original cohort.

And if they have a good relationship with this cohort, you know, given resources, et cetera, then you could enroll that cohort, the offspring cohort, and try and do, you know, an even better job of exposure assessment. That will be out of date in 10, 20 years also but it would be relevant to looking, perhaps, at the reproductive outcomes in that part of the cohort.

CHAIR HEERINGA: Steve Heeringa.

The only difference I would see between Framingham and this study is in this study, enrollment was conditional on a behavior or a practice as of recruitment date, which was that you were a pesticide applicator.

I think Framingham as a general population study so the dynamic recruitment of individuals is sort of conditioned on a pre-existing status and that is your father or your mother was a pesticide applicator. So if we had a lot of -- clearly, you know, the offspring of pesticide applicators or pesticide-licensed purchasers are potentially farmers and pesticide purchasers but there is a whole set of other people coming in whose parents weren't in that category. That would be the difference.

Dr. Gold?

MEMBER GOLD: Yes, I agree that that's a difference but it actually could be a plus. I mean there's sort of different approaches here. I mean the initial approach

was to look at people with a high likelihood of high exposures, mainly applicators. And that has a great utility.

But there's also utility at looking at a broader spectrum of the population in terms of, you know, possible effects of exposure. And I would expect in the offspring you'll have some who are still applicators and farmers and some who aren't. But may still be exposed.

So, you know, I think -- I'm sure they're doing this -- but they could be looking at the relative merits of such an approach.

MEMBER BOVE: Thank you. It could family exposures, right? I mean children are playing around the house and the farm and getting that kind of an exposure. And that's the only way you'd be able to evaluate that.

CHAIR HEERINGA: Other comments in response to Question 4.1? This is your chance to come back.

Dr. Lu?

MEMBER LU: I want to add this disclaimer in terms of what I just said. I think EPA should see these as occupational datasets. They should not interpret them further other than outside of the workplace because sometimes it can get easy to kind of go over bounds because there are significant exposure pattern differences between exposures and non-exposures. And I don't think these things kind of -- they overlap significantly.

And also I would like to ask the panel the question, because I didn't get the chance to ask the Agricultural Health Study folks, is what do you think about a healthy worker factor in the Agricultural Health Study? Would that bias the outcome?

CHAIR HEERINGA: Good question.

Dr. Bove?

MEMBER BOVE: Not if you do an internal analysis. If you compare agricultural workers to the general

population, sure. But if you're doing an internal analysis, it shouldn't.

The problem would be in these studies, the major problem is loss of follow up. When you have a long prospective study, you lose people at the selection bias. I would be more concerned about that.

If you are comparing the agricultural workers to the general population, you really shouldn't be doing that. You know, there's no need to.

CHAIR HEERINGA: So, Dr. Bove, your point about internal is essentially conditioning on the characteristics of these individuals when they were enrolled, the exposure response relationships?

MEMBER BOVE: Hearing high and low, there might be some selectivity and loss to follow up on the health of the individual. But that's a loss to follow up problem, not a recruitment problem.

Loss to follow up is another

issue. I mean I was talking about healthy worker. Loss to follow up is a big problem, okay, and that has to be evaluated in any prospective study. And it could be related to exposure status for sure. And that's a problem.

We were just talking about healthy worker effects and there are several types of healthy worker effects, okay, and it includes not only loss to follow up but within the cohort you could have people who are exposed, highly exposed dropping out of farming, for example, because they are sensitized. I mean there are those kinds of issues. So I guess they are tied -- you can tie them together, sure.

MEMBER LU: I think my -- the issue that I can foresee here is that the healthy worker effects start at the recruitment stage. They are the only healthy workers that they see still working in the field in the farm industry for another 20, 30

years they participate. Whereas people who already have some health problems, they don't do the hard work. And they are not part of the Agricultural Health Study. Would that bias the outcome? It's not the process itself. It's at the recruiting stage, would the healthy worker effect come into play that, you know, make the study --

MEMBER BOVE: Ideally, you'd want to get people as soon as they enroll -- become farmers, right, to avoid that. I mean, you know, you are just starting work at a plant, right? If you don't get people that way, then yes.

he people who are sensitized quit and you lose those people. That also happens as time goes on, too. And, again, that's part of why you have loss to follow up is because people are leaving and you can't locate them. And they are leaving because they're sensitized, yes.

So there are all these -- we

haven't -- I mean there's a whole lot of healthy worker effect biases. It's a whole -- you know, and so -- and this is one of them.

CHAIR HEERINGA: Dr. Reif?

MEMBER REIF: I just want to support what Dr. Bove is saying. If you were comparing this cohort to the general population, of course, farmers, as you point out, are generally healthy. They have to -- they have a very physical lifestyle and job.

And also their behavioral characteristics differ from the general population in that they tend to smoke less. And that was noted in many case-control studies where they -- and also in original descriptive studies where they -- for example in mortality studies, the death rates of farmers from lung cancer and laryngeal cancer and other smoking-associated cancers are lower than the general population.

So that's where the healthy worker effect manifests itself. And it's well

recognized in earlier studies of farmers that they, in fact, have lower rates of cancer for some outcomes, especially the smoking-associated ones, and some higher -- some interesting higher rates of cancer for other outcomes like prostate cancer, which has been described in a number of studies.

So yes, that's where the healthy worker -- that comes in. But with respect to the hypothesis, that agricultural activities are related to cancer risks, goes at that stage, the healthy worker effect, I don't believe is an issue.

MEMBER BOVE: I think it is a lot more complex than that now that I'm starting to think about it, waking up, that, you know, first of all, of course there is the obvious healthy worker effect when you compare a worker population to the general population.

And then there are healthy worker effects that occur in a cohort like the one you are alluding to is even at the start, if

you haven't gotten people -- if you haven't gotten people at the start of their farming experience, some of those people may have tried it, been sensitized, and left. So you're missing those people.

Then over time, people who get sensitized and leave, they have a lower exposure, right? I mean they have a lower cumulative exposure and yet they may have the health effect because they're more sensitive to it and they're also the people you might lose. So there are a whole lot of things going on here that I'm sure the Agricultural Health Study is thinking about.

But these are part of the problem with -- see there are limitations to prospective study. I mean we talk about the length of time you have to wait for results. Now for results that occur quickly, if you're looking at reproductive topics, cancers, things like that, that's one thing. But if you're looking at chronic diseases, it's much

different thing. We have problems with loss to follow-up, you have problems with all of these issues that have been raised.

So that's why, you know, it is one of the better study designs but it has limitations just like other types of study designs whether you use case-control sampling, whether you use a retrospective cohort design, whatever terminology you want to use here, all these studies have pluses an minuses. And there's not one that is going to be terrific for risk characterization, okay.

If you wanted to do a risk characterization today, a prospective study is not what you'd want to do. You'd want to hope that a retrospective cohort study was done at least if you wanted to do something today.

If you want to do something in 30 years, that's a different story. And I think that, you know, you'd plan this -- you can plan this out. Obviously the Agricultural Health Study was planned out with that notion

in mind, that we'd want to have that information 30, 40 years down the pike.

So similarly with Framingham, we'd want to have that information. You don't think it is going to give you information today, right. So anyway, that goes all over the place. Sorry.

CHAIR HEERINGA: Okay. Dr. Bailar, one last comment on this?

MEMBER BAILAR: How do you deal with these issues has to depend on the objectives of your study. With the Agricultural Health Study, there are multiple objectives and it would be hard to sort them out and focus the design on a specific issue. This might be even more true of a new Agricultural Health Study.

But if your interest, for example, is in hazard identification, you might want to focus on workers in the initial enrollment who have been in the profession for say three years, five years, because they are likely to

stay there.

Throwing out the short exposures, you might get rid of some of the ones are highly sensitive but at the same time, you'd get rid of a lot of people who are not going to contribute much in terms of lifetime exposure or long-term exposure. So this is going to have to be given a fair amount of thought.

CHAIR HEERINGA: Thank you, Dr. Bailar.

At this point, I think I'd like to move on. I'll turn, first of all, to Dr. Lowit. I mean I think there has been a good discussion of the properties, generally the prospective designs in the context of the Agricultural Health Survey.

I understand that there are over 100 papers. And I suspect that many of these methodological issues have been addressed there and that you are looking at that, too.

But I think going back to Dr.

Harris's point, I think it really gets down to exposure assessment. And then characterization of risk.

DR. LOWIT: That's a good segue for the next question.

CHAIR HEERINGA: Very good. Would you like to read the next question into the record please, Shalu Shelat?

MS. SHELAT: Question 4.2, The Agency uses a predictive, scenario-based approach to calculate risks associated with the registered use patterns of pesticides. Estimates of risk based on varying levels of protective equipment, application methods, and use conditions are presented. The results of these assessments are used to specify label conditions that are required to support the new registration or continued registration of pesticides.

In contrast, the goal of epidemiologic exposure assessment within the AHS is to develop a relative exposure ranking

of individuals who are actual pesticide users within a cohort. It is not feasible to directly measure actual exposure in observational analyses such as the AHS.

The AHS exposure information is ascertained from questionnaires completed by individual cohort members. Because the AHS and the Agency have different purposes for evaluating pesticide applicator exposure, there are inherent differences in the occupational handler exposure methodologies between the AHS and Agency.

How to reconcile these differences in order to make optimal use of the AHS in developing regulatory policy is under investigation by a collaborative effort between EPA's OPP and investigators involved with the AHS. Case study B details a three step analysis plan for accomplishing this goal.

Please comment on the proposed plan for comparing the exposure assessment

approaches between the Agency and the AHS. Please include in your comments the scientific value of this comparison along with additional and/or alternative analyses which could be conducted.

CHAIR HEERINGA: And Dr. Reed is our lead discussant on this. Ruby?

MEMBER REED: So we're, in a sense, switching mode a little bit. We're adding another component of purpose or desire, looking at the AHS study.

It appears that the method of comparison is illustrated with the Agency's presentation between the groundboom and airblast applications is a reasonable first step. And I was sitting here and also as I was reviewing the Agency document, I was really curious about what is the expected outcome in this comparison.

And then, as you heard, you know, I was sort of drilling down to the difference between 3.7 and 7 in terms of what contributes

to the similarities. But, you know, we talked a little bit about that already. I think there is some common grounds in the database that are used between the two approaches that you could expect some similarities.

But then, you know, you will be doing a lot more comparisons than you could expect to see, you know, in some scenarios. There's wide differences. So I come away with just sort of philosophical within the first step, as you go down on the comparison list, there are scenarios. It is very important to discuss the uncertainties and variabilities in the database themselves.

And also that, in thinking ahead, that if the comparison really gives you a wide variety of differences, you know, as you do these ratios, it might be necessary for you to break out individual parameters in the AHS and to, you know, see if you can find some rhymes and reasons to it.

In terms of Step 2, that's

actually more exciting because now you are looking at biomonitoring data instead of these, you know, category-oriented parameters. And I guess, you know, in that sense you can be more focused in discovering factors that could contribute to the differences between the two exposure estimation methods.

But I really think that if I were to sort of think ahead, I really think that it would be more productive in this comparison for short-term exposure scenarios than going all the way back to the lifetime in all the equations with the lifetime factoring or, you know, long-term kind of scenarios.

Going into Step 3, it's really, really mind boggling with you think of, okay, so now, you know, if Step 1 and Step 2, you know, giving us enough encouragement for us to go on, it's really complex and especially for longer time scenarios.

And so I totally agree that the feasibility would have to be assessed at this

point in terms of how far to go. Really overall what I'm seeing is that, you know, the initial try is okay, making comparison is okay. But I think prioritization is very important because you have two goals and two very good goals.

One is just to look at chemical-specific issue in terms of exposure and health effects and plug that into risk assessment or, you know, make use of that in risk assessment. But the other goal is to see what we can gain from this and back to the Agency's default method of estimating exposure using current PHED or new PHED or, you know, something similar to that.

And so when I think of prioritization, I'm thinking if you get bogged down by these, you know, running the two goals together, I think it is reasonable to narrow it down to, you know, with the priority for one then the other.

And so if chemical-specific

information for atrazine or, you know, any other cases within the AHS, isn't priority, then put the PHED aside as added value and especially because PHED is probably going to receive new information in the future, and so that's sort of my take about the plan, the three-step plan. It's all very futuristic so we would have to see what happens.

CHAIR HEERINGA: Thank you, Dr. Reed.

Dr. Hayton?

DR. HAYTON: I had similar comments on the plan. I thought it was a rational way forward. The first step to do an evaluation of the exposure determinants, that made a lot of sense to me, trying to find similarities and differences in the various elements of the exposure metrics.

I think it is really clear that the two metrics have to be picked apart. And this is exactly what you're intending to do is to look at the various elements and see where

you can find commonality there.

The second step also made sense to use a biomonitoring dataset. And, as I understand it, to apply both metrics, you know, to the same exposure population.

And I don't know about the third step. I just can't comment on that with expertise. But it made sense to me but it is a little outside my expertise.

As far as scientific value, we were asked to comment on that. And I think obviously trying to find some commonalities between the two metrics would be useful if they can be found. The Agency metric connects laboratory studies, connects with laboratory studies. This conceptually allows results of laboratory tox studies to be used to regulate exposure limits, as I understand it.

And that there could be some linkage between the Agency and the AHS metric, then that latter metric likewise could inform regulation of exposures. So there is

certainly value if that can be done.

I didn't have any ideas about additional alternative analyses. One comment in the case study text on page 21, there's the statement that the AHS intensity level score differs from the Agency's exposure algorithm in that it does not attempt to quantify exposure or dose in absolute terms.

And then I looked back a couple of pages and I see that exposure -- I mean there is an explanation of exposure differing from dose in that dose refers to the amount of chemical to which individuals are exposed that crosses the external boundary.

And then I thought about my comment from, I think, yesterday, that even if we know what crosses the boundary, there is a lot of person-to-person variability in what the exposure of target sites is. So all of this led me to think that in a sense, the Agency's metric, even though it says milligrams per day -- it has some units

attached to it -- it's related to internal exposure but I think there are intervening steps that we can link between external exposure and internal exposure. And so it's not a particularly absolute measure of internal exposure by any means.

So also, you know, the other part of this, the Agency's exposure algorithm is not chemical specific but incorporates what is known generically about external exposure, physical state of product, equipment used in the application, protective measures used by the applicator, so sorry to be long-winded about this but this seems similar to me to what goes into the calculation of the AHS metric, too.

So you end up with a number from each metric. And I guess the trick is going to be what, you know, how can -- where is the Rosetta Stone? How can you link one number to the other?

But I think it's plausible that a

way can be found to make these metrics talk to each other. I think that's true.

CHAIR HEERINGA: Thank you very much, Dr. Hayton.

Dr. Harris? Shelley?

MEMBER HARRIS: Well, I don't have a whole lot to add. I had a little difficulty getting through the document. I'm a little bit confused -- had a hard time following it.

I think -- I probably have more questions than I have comments on some of the statements. I'm not sure if this is -- should we wait until after or --

CHAIR HEERINGA: Why don't you go ahead?

MEMBER HARRIS: Go ahead? So I think I have a fairly good grasp on the AHS and the intensity score and how that is derived and what they plan to do with that for coming up with some sort of ordinal ranking of exposures based on different categories and classifications. So I'm fairly clear on that.

Now the Agency's methods of assessing exposure, I've got down here -- I've got milligram per day measure. Is that something that is assumed to be an absorbed dose? Is that the way you are doing that?

CHAIR HEERINGA: Jeff Dawson?

MR. DAWSON: I'm Jeff Dawson. We would predict exposures -- it would be the amount to the skin. And then depending upon the nature of the endpoint, we would be using for risk assessment -- for example if we were comparing to a dermal administration toxicity study, we would just use that value.

If there was, for example, an oral administration study, we would apply some factor to account for dermal absorption to get to the absorbed dose. So when we talk about exposure, we're talking to the skin or --

MEMBER HARRIS: So you have a milligrams active ingredient per day? So that would be a dermal dose? And then you could apply some percent absorption and calculate an

absorbed dose with that? So that's --

MR. DAWSON: Correct.

MEMBER HARRIS: -- so you use the PHED and other databases to come up with those estimates on a daily basis? And then you multiply those by duration and things like that? I think lifetime exposures to come up with that? Is that --

MR. DAWSON: Correct.

MEMBER HARRIS: Correct, okay.

MR. DAWSON: So PHED provides an amount to the skin, for example, per pound that you apply. And then we use the knowledge about the cultural practice to represent each of the different scenarios for equipment type and the crop that's being treated to get to that daily dose estimate which, in effect, accounts for duration.

MEMBER HARRIS: Okay. Because a lot of my question is really how do we connect these two different exposure measurement techniques and I think the assumptions that go

into yours and the assumptions that go into the AHS are extremely important in doing that.

I also had another question about this unit exposure measure that the Agency -- and I wasn't quite sure I understood that because in a couple places in the text, you talk about equivalency between chemicals so assuming the same kind of active ingredient apply.

But then -- and I understand that -- but there was another statement about looking within a chemical if you would double the application or double the amount applied, did you assume a double dose. And that was like a linear relationship. And that's something that I would probably dispute. But I'm wondering if that's an assumption.

MR. DAWSON: That is the assumption. And actually over the last couple years -- and I know for example Dr. Chambers has heard a lot about this because we've presented a lot of this issue to the HSRB with

our new study designs and also we talked about this some in the 2008 SAP, I think, where we talked about handler risk assessment methods, so we assume that linearity -- and there is some variability around that assumption -- and so with the data, we're attempting to evaluate that linearity as much as feasible with the new data.

So -- and what we see so far when we look at that is when people get higher and higher exposures, there's some kind of asymptotic relationship so we believe that assumption of linearity is actually somewhat conservative for the higher exposure folks.

MEMBER HARRIS: It's interesting in some of the occupational work we've done in different cohorts that we're finding -- in pesticide applicator cohorts, finding very little relationship between the amount of pesticide used or applied and the absorbed dose estimates, sort of on the level of, you know, 0.2 -- an r-squared of 0.2 or so. It's

quite, quite low.

We're finding that the other factors, the protective equipment factors are modifying that relationship between the amount used and the absorbed dose quite significantly. But I think that the pharma cohorts are a little bit different. I think it is probably more linear.

MR. DAWSON: Oh, and we would definitely agree that the use of protective equipment would significantly modify the exposures. And that's reflected in the measurements that we have, for sure.

MEMBER HARRIS: And so -- and also how much -- I know that some validation studies have been done with the PHED data or using biological monitoring. I'm wondering how much?

MR. DAWSON: That was actually one of the topics that we brought to this panel in 2008.

MEMBER HARRIS: Okay. So I'm

probably asking some of the questions from a few years ago. Okay, okay.

So I ask that because I looked at the Agricultural Health Study and I looked at what kind of biomonitoring they have done in relation to trying to validate their measures. And I think that that's the natural connect -- that they use the biomonitoring from the two different approaches and seeing how those relate to the exposure estimates. And then you can come up with some estimates of error and try to connect the two.

MR. DAWSON: I think that's definitely one of the issues that we will be looking at in the second phase of our approach.

MEMBER HARRIS: Okay.

MR. DAWSON: And just so everyone is clear, the unit exposures, we basically treat those generically because we believe if you use the same equipment, go apply the same field, whether you have, you know, Chemical A

or B in the tank, if you apply the same amount, that the exposure rate you are going to get is the same. And it's driven by the kind of the engineering aspects of how you make the application. And it's just to the skin. We evaluate it based on that.

MEMBER HARRIS: And so the only other thing I would add is that I think there is an opportunity in the Agricultural Health Study and I know the cohorts aging is not only just to go and do some validation but to go and do some predictive modeling of absorbed dose. And by taking samples within the cohort and using either the existing questionnaire or newly-obtained questionnaire information on their spraying practices and hygiene and behavioral characteristics and that type of thing. And trying to predict models of absorbed dose that you can use with the other applicators.

So it may be based on existing -- if you want to apply it to the entire cohort,

it would be based on existing data that's collected, yes. Thanks.

MR. DAWSON: I would say we definitely agree with that. And those are the kinds of things we're thinking about for the Phase 2 and then when it got into the more chemical-specific aspects of Phase 3 based on what we learn.

MEMBER HARRIS: Thanks.

CHAIR HEERINGA: Thank you, Dr. Harris.

Dr. Bailar?

MEMBER BAILAR: I have very little to add. I think this has been a good discussion.

There is one thing, though, that concerns me. Like Dr. Harris, I had a lot of trouble understanding this. I had to read parts of it three times. So I recommend that the whole thing be rewritten for clarity. And that you add an abstract that's written for maximum clarity for people who are not on the

inside, who don't know the subject, think, you know, of the Congressional staffer who is not very far out of college with a degree in sociology. Would they be able to understand this? Not a chance.

MR. DAWSON: We appreciate your candor. And that's definitely something that we struggle with on a daily basis, absolutely.

CHAIR HEERINGA: We went through the SAP on the ag handlers exposure. And you've got to go back to high school chemistry and remember your method of units or you can't keep track of anything. So very good.

Dr. Greenwood?

MEMBER GREENWOOD: Again, I've not go a lot to add to this but I think part of the difficulty in trying to compare these two methods is that both of them have got a series of steps. And maybe you need to do some sort of sensitivity analysis to see if there is a discrepancy, where is it coming from? What's the weighting of these various steps?

Because what you've got is quite a difficult set of data to untangle. And I think as other people have said, you will have the opportunity if you've got some biological data to have a common -- a connection between the two.

But I don't think that will make it immediately obvious as to which parts of the two algorithms are actually generating any observed differences. So I think you will probably need to look very carefully at the impact of the different components in the algorithm.

CHAIR HEERINGA: Comments from other members of the panel?

(No response.)

CHAIR HEERINGA: Just out of curiosity, the one sort of case that you've done where you had 3.7 and 3, that's a fairly high level of agreement. Was that sort of an easy pick? Or was that a random choice?

MR. DAWSON: No comment.

(Laughter.)

CHAIR HEERINGA: I'm not being judgmental. I'm just trying to establish --

MR. DAWSON: There are definitely ones that we've looked at where there is a great diversity.

CHAIR HEERINGA: We would expect that in Dr. Reed's --

MR. DAWSON: And if you recall from like the 2008 -- within that PHED data, there is a wide range of -- that you see in the results. So we'll be looking at that, trying --

CHAIR HEERINGA: -- you know I think Dr. Reed's and Dr. Greenwood's point -- Dr. Hayton, too, everybody is sort of, you know, getting at the components of each of these final estimates.

Other comments from panel members? Dr. Reed?

MEMBER REED: Well, we've talked so much about what's in the future in

distributional analysis and what can and cannot be done within PHED, I just want to put that in the record and I think it is a good one.

MR. DAWSON: Right. Absolutely. And within the new dataset that we're working on generating, that will give us more ability to look at the issues of accuracy and uncertainty and variabilities. So we're very hopeful about that.

CHAIR HEERINGA: Steve Heeringa. I would just add, too, you know, I really support this effort because those of us who've been party to hearing the presentations on the Agricultural Handlers Task Force and all of that work that's going in there, we all recognize that the expense of collecting that type of data any way we can gain of amplifying our estimates of exposure under these different scenarios, maybe by borrowing strength from the two data sources, it's clearly a benefit.

Dr. Lu?

MEMBER LU: I was reading the question and I just want to emphasize the scientific value of this comparison of this activity is huge. It is because the cost to do the study again and so on and so forth but I would not use comparisons because it is really orange to apple.

Instead I would say using the data collect by the Agricultural Health Study into the regulatory arena and using the regulatory standard to come up with the measurement, I don't think comparison is a good word.

CHAIR HEERINGA: Dr. Reed?

MEMBER REED: Just one comment. Before Jeffrey mentioned that with the new data, that he can do better comparisons. When I'm talking about distribution analysis, I'm actually talking about what you are about to do in terms of comparing the AHS. And PHED, it's occurring in PHED. And that you still have some ability to do distributional

analysis, not waiting for the new database. Is that what you were referring to? The new database? Or current database?

MR. DAWSON: It would mainly be on the new database. But we're going to try to incorporate as much distributional elements as we can in the other aspects of it. For example, I think it's more readily accessible on some of the exposure factors information, for example, that we could glean from the questionnaires about the use patterns for the individuals.

MEMBER REED: The other sort of follow up with Dr. Lu's comment was that when I said that when it comes to something that is entirely too complex for you to, you know, chew through, I was talking about setting priorities perhaps, you know, on chemical-specific evaluation, specific to whatever chemical, atrazine or anything that you want to look at.

I'm also thinking of the ability

to fine tune or improve on the use of PHED-type of data when the new PHED data comes. And so the comparison between the old and the new might reveal a lot more than, you know, this particular plane of comparison. I guess I need to clarify that. Not to put PHED evaluation aside as if it's not important.

CHAIR HEERINGA: Steve Heeringa. Was it not correct that some of the studies that are in the current PHED will be brought forward into the new database as well following an evaluation?

MR. DAWSON: Very limited number.

CHAIR HEERINGA: Okay.

Dr. Portier?

MEMBER PORTIER: I have to admit I didn't read this document that carefully but I was just looking at it and in Step 1, you state the overall objective of this kind of analysis is to evaluate whether or not there are differences in the predictions for exposures, regardless of approach, right?

So you're going to be kind of -- you're trying to relate these to it. Again, I get the feeling that you are trying to relate point to point on an individual basis. And you might actually want to back away and think in terms of distributions and say can I get the distribution from this population from the Ag Handlers Survey to match the distribution from a scenario approach, right?

I don't know. That doesn't -- that kind of concept doesn't seem to be in this writing. But I think you understand what I'm talking about there.

MR. DAWSON: I think your point is well taken. And I think that was -- we didn't articulate it well but we wanted to start with the simplest and then move to that. But --

CHAIR HEERINGA: Dr. Bailar and then Dr. Chambers?

MEMBER BAILAR: Well, I would not abandon the point-by-point comparison. There might be a lot to learn from those subjects

that are high on one and low on the other versus the ones with the reverse.

CHAIR HEERINGA: Especially on the sensitivity parameters.

MEMBER BAILAR: No, it would be a good way to find out which one might be more closely related with outcome.

CHAIR HEERINGA: Dr. Chambers?

MEMBER CHAMBERS: It occurs to me during this discussion -- excuse me -- that the reason for the Ag Handlers Task Force updating those data is that the PHED data is based on more historical types of equipment and that sort of thing when the exposures may have been higher because currently there are more protective types of spraying exposure -- or of apparatus and what have you.

So in trying to do lifetime exposures with this, that creates a challenge. And I don't know how you are going to deal with that. The exposures may have been higher in the past than they are currently. So you

may have to kind of lend a differing exposure assessment into that for several years ago to when the equipment changed more recently. Am I making any sense? I guess -- you're nodding.

MR. DAWSON: No, I think you are. And I think just in general as we transition, we're going to have to understand that element of it. And, you know, try to be very thoughtful about what's -- how the new data will be representative of agriculture now as its practice in all its forms.

But that's a very good point. I think in certain cases where, you know, there might be higher exposure scenarios, we might prioritize there and look at, well, how did airblast technology change over time or something like that. That's a good point.

MEMBER CHAMBERS: Because in follow up, the point of the Ag Handlers is are workers being protected at present with the current protective measures and that sort of

thing, right? Not to estimate lifetime exposures. So it's very different goals.

MR. DAWSON: I would think that's a fair -- we would use it to predict lifetime exposures but it would -- I guess the way you first described it is we want to capture current cultural practices would be the way to describe it.

CHAIR HEERINGA: Okay. Dr. Greenwood?

MEMBER GREENWOOD: One way that you might get something useful out of the comparison when you do the plot is if you can identify in that plot where different levels, using the HS classification, you can maybe identify the different categories and see how they map onto it.

It just occurred to me that may be one way of getting a reasonably easy picture because if you do start to see separation in there, it may also explain if you've got discrepancies between the two methods.

CHAIR HEERINGA: What I'd like to do at this point is call a break until ten minutes after ten. And at that point, we will reconvene and address the final charge question and wrap up. And I think we should be finished before the noon hour. I want to thank everybody for their comments this morning.

(Whereupon, the foregoing matter went off the record at 9:53 a.m. and went back on the record at 10:13 a.m.)

CHAIR HEERINGA: Welcome back. Just one more reminder to the panel. Make sure you bring the microphone very close to you even though up here it sounds like we're plenty loud, I think with the vibrations generated by these video screens here, it is sometimes hard to sort of discriminate your talking in the back. So make sure you get the microphones very close and speak loudly into them.

At this point in time, we are on our last subpart, Question 4.3. Again, questions related to the application of the Agricultural Health Study in the context of both exposure and risk characterization. And Shalu Shelat, if you would be willing to read the final question into the record please?

MS. SHELAT: If it is okay with the panel, I'd like to make a clarifying statement at the end of the reading of the question.

Question 4.3, the Agency has a long-term goal to understand the extent to which findings from the AHS are generalizable to other populations, such as pesticide applicators in states other than North Carolina and Iowa or those who may be exposed to pesticides through other pathways under different use conditions. Please provide suggestions for analyses which could be conducted to make best use of the results of AHS in a broader regulatory context.

As a clarifying statement, based on the discussions we've had with the panel, we'd like to make total utility of this information that is provided to also be considering generalizability in terms of bystanders as well as general population. And if there is anything anyone else would like to add to that?

MR. DAWSON: Just -- and also because we focus our case study in occupational handler in part but there are other people involved in the cohort. So we want to make sure that we ultimately make as much utility of that information as well.

MEMBER REIF: Can I just ask what do you mean by bystanders?

MR. DAWSON: That's -- there is a broad definition of bystanders but, for example, probably in the context of the Ag Health Study, it's the farm family folks who are living with the applicators and, you know, whoever they might be involved with in that

cohort. So to the extent possible, their children, those kind of --

MR. DAWSON: Just to clarify, with response to Dr. Lu's comment earlier, some of the Agricultural Health Study cohort members are not occupationally exposed on the farm. Those spouses, for examples, but the children are not -- as far as I know, are not considered directly as part of the cohort. They might constitute bystanders. But the non-employed spouses of the applicators are, in fact, in the cohort.

CHAIR HEERINGA: Our lead discussant is Dr. Harris.

MEMBER HARRIS: Thanks. Thanks. And I'll just follow up. Can you just read that statement one more time. You said you were interested in the generalizability for bystanders as well as -- and I missed that last part.

MR. DAWSON: The general population as much as feasible with this

dataset.

MEMBER HARRIS: Okay. Well, I appreciate that clarification because I wondered if you wanted us to even venture into that territory at all with that question.

I'll just start with saying --

DR. LOWIT: Just maybe one more big picture thing. Something that we've thrown around the idea is handlers in the Ag Health cohort, handlers in other states, post-application markers, farm families, the general population as you get further and further away from the cohort, how far then do you stretch that data? That's the sort of things that --

CHAIR HEERINGA: Like the low end exposure pyramid.

(Laughter.)

CHAIR HEERINGA: Dr. Harris?

MEMBER HARRIS: Okay. So I read a little bit of that into the question and so I'll attempt to give you my thoughts on these.

First of all, it is a difficult question because -- for a number of reasons. But when you talk about generalizability or how we can generalize results from the AHS to these other populations and once you get further and further away in exposures, I'm assuming that you're talking about past exposures? Are you talking about other exposures? What kinds of outcomes are we talking about here because how we generalize will depend on the outcome of interest.

And so if it is a cancer endpoint or a respiratory endpoint or a cardiovascular, whatever it may be, it may be more difficult to translate these findings to other populations, other geographic locations, and, again, that's an outcome-specific thing.

So I would -- you know, my focus would be looking at the effect of pesticides with cancer and frame the comments a little bit better that way. So if that's one of the priority outcomes that you'd be looking at.

I think -- so first of all, if we were taking -- if we're trying to generalize the results of pesticide exposures and the cancer risks to other -- what's your first level here -- other pesticide applicators in other states -- then I think that would be more of a direct -- it would be easier to do and easier to generalize.

And I think making the assumption that we're dealing with similar doses so I realize the pesticide application patterns and seasonality and things like that vary within the United States or even internationally -- certainly internationally. And so those things would be taken into consideration. So variations in dose.

But you probably can, given certain racial and ethnic backgrounds and mixes, generalize to other states, again, it depends on the cancer, it depends on the pesticide, and it depends on whether there are any kind of interactive effects or synergistic

effects how well you could do that because there is quite a variation across the United States and that kind of make up.

I think the next question was -- oh, exposed to pesticides through other pathways and under differing conditions of use. So primarily we're looking at dermal exposures in this setting for the Agricultural Health Study and so can we translate these findings for oral exposures or inhalation exposures?

And maybe in this case you're starting to move towards the residential and bystander exposures. I'm not sure what you're getting at with this question. But, again, if we assume that we have a similar age group and a similar ethnic or racial makeup and similar internal doses, that it wouldn't be too difficult to generalize those results. That's my first thought on that.

And then we move down to -- okay, so then you'd expand the question a little bit

-- so generalizability for bystanders, general population, farm families, children, et cetera, so we've got our occupational exposures, our applicators with the highest potential levels. And then we have bystanders -- I took that -- I mean you would have bystanders in occupational settings and bystanders in residential settings so like it all depends on how you define it.

But I would look at exposures probably decreasing from the occupational to the worker bystanders, like migrant farm workers, whatever they may be, to potentially spouses on the farm, children. And I would expect those exposures typically would be higher than those you would observe in residential settings. And residential applications may be a little higher up there individually but not over seasonally lifetime cases of exposures.

So, you know, the degree to which the age S results are generalizable to these

populations which have much lower exposures, is a very difficult question. And then also we're dealing with adult versus childhood exposures and susceptibilities and that type of thing.

So my guess is that that will be something that will be done on a case-by-case basis. So, again, it's difficult to come up with a broad answer. But I think I'll step back from there and let the rest of the panel address that one.

But we all know how difficult it is to extrapolate exposure in occupational settings down to residential and make that information relevant for risk assessment.

I'll just move on to the second part of the question, for suggestions for analyses that would make the age in a broader regulatory context. And this is not my idea. This is something that I talked to Michael Alavanja yesterday before he left. And I'm not sure if he has called in today or not.

But I just want to put it out there and I have to find it. He said one of the things that didn't occur to me at all was that they have these HPEE and they're called high exposure -- high pesticide -- thank you -- - exposure events. And he said there were a number of applicators in the cohort -- and I didn't get an exact number from him how many people reported these but my guess is it is, you know, maybe ten percent. I'm just guessing, you know, you probably experience these fairly frequently.

And he said of those people that reported these high pesticide exposure events, approximately 20 percent of them had symptoms, chronic neurologic, respiratory such as wheeze, and detached retina, interestingly, and -- but less than five percent were reported to healthcare providers. And that's their data that they've collected.

And so going back to one of the questions with the diazinon, the database,

that case example, it really would be interesting to take that data and look to see if you could link it all into any of these databases, either reported by industry or the poison control or -- I'm not too familiar with those databases -- and what would be key is the type of personal identifying information that is collected in those databases. And that I'm not aware of.

So, you know, it would be interesting to link those databases if at all possible and also to try to link them to reports in the AHS, given the appropriate ethics approvals and that type of thing. So that was one of his ideas -- one of his suggestions on making use of the AHS data.

And I'll let other speak.

CHAIR HEERINGA: Dr. Greenwood is our next discussant.

MEMBER GREENWOOD: I think that to some extent the answer to this question will depend on the outcome of the earlier studies

because it will depend to what extent, I think, that you can produce a common algorithm that is applicable.

And certainly the same categories I don't think would apply to people who are not handlers and so on. And certainly at the moment I don't think that the Agency's algorithm would cover this adequately.

So I think you probably would have to think about developing a modified algorithm. And, again, before you started to move outside the cohorts for which you've got a lot of information, I think you'd certainly need to do a sanity test.

And you'd certainly need, again, I think to spend some money on some biological data in terms of exposure because at the moment, what you're looking at in the earlier parts of the -- the earlier questions this morning, is how can you compare the two algorithms, what can you achieve with them? Will they be equivalent? What can you -- or

where can you take that in terms of maybe producing something which involves both of them? And looking at populations.

And I think probably -- and talking to Dr. Portier while we went for coffee, I think his idea of introducing the study by looking at populations rather than individuals -- getting hung on individuals -- and then starting to look at which of these categories are actually going to give you the sort of measure of biological exposure -- which ones are really going to be important for you to measure?

But I think in order to extrapolate or go outside to handlers and so on, you've probably got -- by the time you finish doing that work, you'll have an easy mechanism. I think you can do that because you won't have to modify things very generally.

But I think as soon as you want to start moving out to other categories of

exposure, then I think -- or roots of exposure, I think you're certainly going to have to rethink the algorithm.

But I think that you'll have enough experience by then to be able to identify which are the more important variables to put in there.

CHAIR HEERINGA: Dr. Hayton?

DR. HAYTON: I found this question a little difficult to address. In terms of extending to other states, I thought the approach could be along the lines of Step 2 for trying to compare the Agency and the AHS metrics. And that is to look at a common population and try, you know, try the two methods on those two populations.

And I don't know if it is feasible to think that way but, you know, take a population from North Carolina and/or Iowa and then as far as going to other states, why not try to find a similar population and, you know, see how that works along the lines of

the Step 2 plan.

And in terms of going out from applicators to other populations, it seems to me that the intensity level metric does have flexibility to handle multiple pathway and use conditions. And if novel situations arise, it seems to me you just have to modify or add determinants of the intensity level calculation to accommodate those novel situations.

That's very general and it may be a lot easier suggested than done but it doesn't seem to me that you are limited with that AHS metric to just the particular facets or subcategories that make up the calculation at the moment.

CHAIR HEERINGA: Dr. Portier?

MEMBER PORTIER: I wish I had another hour to think about this.

So -- yes, it doesn't always work -- yes because the last question has brought up all kinds of ideas. I mean you start

thinking about these things and Dr. Greenwood and I were talking at the break and thinking through this.

And I agree that the answer to the last question where you link the AHS intensity metrics with some kind of a distribution of personal exposure values, right, that's kind of Step One. And then you have to take these intensity metrics or these categories and link them to demographic conditions in the sample so that you can link them back to demographic scenarios in other states and other populations.

Because from my thinking, it's a little bit like a stratified sampling approach. You are going to be defining strata based on these demographic or other characteristics. And then you are going to use something about what this intensity metric translates to to apply them to those strata. That's the only way you are going to be able to extrapolate that out again.

I don't know how successful you are going to be able to do it. I'll try to write this up a little better than I'm saying it so it will show up.

But I mean there are -- you know -- and Dr. Heeringa can probably speak to this -- in the sampling world, there are techniques of taking data on subpopulations and trying to rationally extrapolate that out, generalize it to the broader population. But you can only go so far.

You know the problem I had with the AHS is that it is a high exposure population. So when you start trying to extrapolate that to low exposed individuals, you don't have a lot of information from the cohort to make that relationship, right?

The nice things is that's not the people you are that worried about, right? You are worried about the high-end exposure from a public health and safety point of view. So you've got the right population.

I'm going to stop at this point. I'll write something together.

CHAIR HEERINGA: Dr. Harris?

MEMBER HARRIS: I'll just jump in because I think we answered two entirely different questions. Are you talking about generalizability of generalizing the results of the AHS let's say cancer risk estimates to others? Or are you talking about generalizing results as a comparison of the two exposure metrics to other populations? Because I think we've -- between the four of us, we've answered both of those somewhat.

MR. DAWSON: I say no reasonable offer refused.

(Laugher.)

MR. DAWSON: So actually you could think about this question, I think, in both ways. So it's -- and we struggle with this so I think it's good that people are thinking about it at different levels.

What -- I would like to add one

clarification on -- it probably was not clear at all or even mentioned in our document as far as kind of the other populations that we look at in risk assessment. For example, for folks that go in and harvest crops or kids that are playing on lawns that get exposed. We actually have developed and used exposure metrics for those kinds of scenarios as well.

So part of the discussion, we already have something we can build on there. So the good part about it is, we don't have to go and create all of that for this aspect. We can just kind of build on it like we would with the PHED and the replacement data as well.

CHAIR HEERINGA: Dr. Lu?

MEMBER LU: The farm family, including kids, has a high exposure was the hypothesis in the `90s. And there are actually many studies shows that those kids, if you are comparing their exposure to city kids, their levels are not necessarily higher.

So I mean the statement that Dr. Portier just made in terms of you are comparing -- you have data from the very high exposure group to a very low exposure kid, I don't think we have any data to say that's the case. Pesticide applicator may know how to protect themselves very well in terms of farm pesticide exposures. Whereas citizens living in Crystal City just part of a pesticide just over-spraying his lawn. And it's really case by case, right?

And my comment on this question is you can't do it because exposure pattern is different. Pesticide use is very different. And the pathway is very different.

I understand why EPA wants to do this but the reality is you can't accomplish what you want. You may just focus on your resources and do a good job on categorizing occupational exposure.

CHAIR HEERINGA: Dr. Gold and then Dr. Reif.

MEMBER GOLD: I'd like to interject a note of caution about the generalizability not being an exposure assessment expert. So I'll put that caveat in there.

But I think there are two aspects to this. One is I think that if you think about the crops to which these agents are applied and the say weather conditions under which they are applied, they are very different in Iowa than they are in other parts of the country or North Carolina. So that's cautionary note number one.

And cautionary note number two is as I mentioned yesterday, the samples being studies in the AHS are fairly uniform -- not completely. In California where I come from, that's not the case. And certainly the farm workers who enter the fields after the applications are a very diverse population in terms of susceptibilities and so forth.

And so my note of caution comes

from those two sources. That I think the applications are different. And I think the populations are different. And the susceptibilities in those populations are different.

And I would be very cautious about generalizing from the age as to other populations. That said, I don't know if you have other opportunities, you know, where you could garner some additional information. And I think the answer to those cautionary notes is not necessarily found within the AHS.

Certainly the second one isn't. The first one perhaps you could be enlightened by some of the data that you have in the AHS. So I would just -- I guess I'm at a little bit of a disagreement with my colleagues around the table.

I think I would be remiss, being from California, if I didn't say something about the diversity of the population. And I think the AHS is pretty uniform. There is a

little more diversity in North Carolina but it still is nothing like what we have in California.

MEMBER BOVE: I have a question. It goes back to something that I do in my spare time, which is work with farm --

CHAIR HEERINGA: Dr. Bove, pull your mic up real close.

MEMBER BOVE: -- work with farm labor organizing groups. And there is a very strong farm labor organizing group in North Carolina. In fact they just won a union a couple of years ago.

And so my question is that there are these diverse populations in North Carolina of migrant farm workers, particularly in the pickles in a couple of other crops. But they're not picked up in the Agricultural Health Study. Or are they? They're not. That's unfortunate because then some of the issues that Dr. Gold just raised could be addressed. So that's something to think about

because, as I said, there is a large migrant population in North Carolina that could be evaluated. But difficult because they come back and forth between here and Mexico.

CHAIR HEERINGA: Jeff Dawson.

MR. DAWSON: And definitely we're interested in looking at those populations and kind of review this as methodologically what can we learn about how to do this and begin to look at other sorts of epidemiologic data to do that kind of analysis. Absolutely.

CHAIR HEERINGA: Dr. Lowit?

DR. LOWIT: I think not to get us off on track but just as a natural add-on to what Jeff just said is as some of you are probably aware, that EPA and NEIHS have several cohorts of mother/children pairs, two in Harlem, one in California. The one is California is the so-called Chemakus dataset cohort of somewhere between 300 and 400 primarily Mexican-born farm workers. And there's lots and lots of very rich data coming

from all three of those cohorts that we're very interested in using in other things that we're doing.

So a lot of the things that we're talking about here, even on the Ag Health Study because those are also prospective cohorts, really applies to the way that we're thinking about those cohorts, which are on acceptable populations. They're on lower income. The Harlem populations tend to be lower income. They are people who live in housing -- urban housing. And the Chemakus is primarily farm workers.

So we're talking a lot about Ag Health here today but there are other epi studies that we're extremely interested in. And will probably using over the next year.

CHAIR HEERINGA: Dr. Lowit, just out of interest, what data are you gathering on those cohorts? Do you get drinking water concentrations? Do you get blood? What are --

DR. LOWIT: It varies. The three cohorts are actually very nicely complemented. And some of you may remember from a couple of summers ago where we talked about the chlorpyrifos dataset because the Columbia University cohort is one of those three.

And it varies by the three. And I might have misspoken but certainly they all have urinary measures in moms and in kids. There are some blood measures. They've done some things at birth. They've tracked -- the mothers were recruited during pregnancy. And so they're tracking the children from birth.

A lot of the kids are now in the -- - five to seven years old. So it's actually a really rich dataset, particularly when you put the three together.

CHAIR HEERINGA: Dr. Reif?

MEMBER REIF: Just briefly, I think first, you are absolutely right. This is an important question to raise.

From my understanding of the

Agricultural Health Study, there was considerable thought put into the selection of the two states because of the diversity of agricultural practices. And I agree with Dr. Gold that California would have been an excellent third state because there are clear differences in agricultural practices as well as in the demographic characteristics of farmers and farm workers in that state.

That said, I mean there are a few sort of straightforward approaches where the data permit. So looking at the -- in the first steps of whether data are generalizable, for example, first comparing findings for the two states with respect to a common chemical exposure, second, again, where the data permit, doing stratified analysis, Dr. Portier says to compare the effects, for example, in a Caucasian population and in an African American population, which one could do probably in North Carolina.

So those are some initial steps

that can be taken. And I'm sure will be taken in any publications that come from the AHS or should be because those are sort of straightforward steps that we would always apply to the data analysis to look for that internal consistency across racial subgroups, gender, age, because that's kind of an important biological question is if a pesticide is active in increasing risk, is the risk uniform across the strata of age? Is it uniform across the strata of gender? And is it uniform across strata of ethnicity or race?

So there are some internal checks that can be done and I'm sure would be done. The limitation is that if there aren't adequate numbers of persons in the cohort, particularly of diverse racial and ethnic groups, then the ability to test those internal hypothesis is limited by the distributions of the cohort.

CHAIR HEERINGA: Dr. Bailar?

MEMBER BAILAR: I think I agree

with Dr. Gold. The human biologic responses we're interested in depend on the details of exposure and on the demographic characteristics of each exposed person. They certainly don't depend on state boundaries.

And if I were starting over on this, I'm not sure I would use state boundaries as the primary limiting factor. What matters in a sense is agricultural areas.

And I would like to have the data on perhaps subareas of states that could be separately analyzed and then build those up to get a composite for the state rather than start with the state as a whole and try to break it down.

CHAIR HEERINGA: Steve Heeringa. I'll add my comment.

I would also support, I think, Dr. Gold's caution, particularly going vertical in the pyramid because I know the extrapolation from this data, it's the same issue we face when we talk about the agricultural handlers

task force issue.

You know you get so many scenarios to essentially define parameters. But to any extrapolation or implementation of that data requires a set of model assumptions. And I agree that I think the geographic constraints is really one of agricultural practice and differences, you know, among the states.

That can be handled by, you know, potentially in a model framework by some stratification, getting down to levels where you assume that you have some homogeneity. But that would, in my view, apply to applicators and people who are actually working with this.

To then extrapolate exposures from what we see there or what we estimate there to children, to spouses, to neighbors, even to people working, I think that requires another set of data. And I don't see that data in the Ag study.

It may be -- some of it we're

talking about it coming from the applicators, you know, the task force datasets in terms of, you know, variability among applicators.

But there is a big jump when you start -- I don't deal with a lot of this data but I've seen data on dioxin, which would be intensively looked at both in environmental measures, individual measures, family measures, soil measures. And there is a lot of heterogeneity in these data.

And the differences, you know, I think it was mentioned with regard to children and households, too. Dr. Lu mentioned it. I don't know what that mechanism is but I would assume the extrapolation from the applicators that we're studying, the farmers who are making the application even to the next level of their children and their spouses, it is a different mechanism of exposure.

And so I don't think you can generalize the exposures. I don't know once the exposure happened, maybe you can

generalize the mechanism. But I think you have a real challenge in generalizing the exposures.

Anybody want to react to that? Dr. Reed?

MEMBER REED: I agree with you.

CHAIR HEERINGA: That makes me feel very good. Thank you.

MEMBER REED: Sorry. I mean -- no, I agree with you. And the reason is because you have different currency. You have different algorithms in calculating or estimating the exposure. Just about the only thing that is shared is the use pattern.

But you have far more differences than -- I mean different parameters than just use patterns. And so that extrapolation certainly would require far more than just AHS studies to allow you to do that.

So actually when I was reading the framework document and you said, you know, you future sort of goal is to extrapolate from the

applicators to even just all agricultural workers, I said no, that must be a typo from applicator to applicator, yes. You know there is that possibility.

And so if we're talking about farm families and children and even bystanders, non-occupational bystanders, that is a totally different kind of algorithm, you know. I would encourage that the Agency map out what exactly you were thinking of instead of just sort of free floating idea. What is your current practice? And at what point where thing a bridge can be connected?

And I think that would help in this discussion much better, I think.

CHAIR HEERINGA: Just to sort of restate my comments -- Steve Heeringa -- I think the potential for sort of geographic extension of your inference or, you know, focusing on subgroups that are represented in the North Carolina and Iowa samples, even though they may not generalize to the Central

Valley, I think there is a little more potential for that than going vertically in the pyramid. But again, I want to defer to the real experts here.

Other comments? Shalu? Oh, Dr. Greenwood?

MEMBER GREENWOOD: I think that was what I was trying to say in my clumsy manner. That you'd need to do a whole lot more development work if you wanted to move to other groups. You'd have to establish, again, the populations in the same way that's been for the applicators and users.

And I think if you wanted to put the effort into that, then you could certainly move that around, I think, as well. But you have to look at a whole new set of -- a whole new approach, I think, to a whole new set of maybe sources of contamination associated with behavior of the applicators and so on.

And that could be difficult because I think people are going to be less

open and honest if they feel that they are contaminating their kids and their wife.

CHAIR HEERINGA: Thank you, Dr. Greenwood.

Other comments on this issue? It's obviously -- Dr. Bailar?

MEMBER BAILAR: It isn't directly on this issue. I'd like to go back a bit to the comparison of the two metrics.

As I understand it, you're doing it for every person who is in the study? You want to have the two metrics for each of the subjects?

MR. DAWSON: Jeff Dawson. I'm not sure we would commit to every person in the study but perhaps a subset at some point. That we would definitely be interested in doing that for a subset of them. And as far as the scope of the exercise, I think it will be -- we view this as an iterative process so as we kind of march along our plan and as far as the resources and such allows, I think, you

know, we'll try to do that as much possible.

But there may be a point where it is a diminishing return or something. So we'll just have to kind of evaluate that as we go. But I would say we probably definitely would not for every person but probably selected subsets is my guess.

MEMBER BAILAR: Well, selected subsets would be helpful. But even with that approach, you might learn very nearly as much by looking at truly random samples. They don't have to be simple randoms. You could use stratified random, random according to, you know, well you might want to talk to a sampling expert about it.

But do it for a random subset and that will tell you -- first give you the characterization of the relationship between those two. And even if you are interested in specific outcomes, relatively uncommon outcomes, you could do it for 100 percent of the people with that outcome and a random

sample of the others.

You know if you try to do it for everybody, you'll end up with a ratio of cases to controls of one to 100, one to 1,000, maybe one to 100,000. And that makes absolutely no sense statistically.

So you might want to think about, you know, getting some help in doing this on a random basis.

MR. DAWSON: No, I think your point is an excellent point. And to the extent you can incorporate that into the discussion, I think it would be very worthwhile for us.

CHAIR HEERINGA: Any other comments on this final part of Question 4 from the panel?

(No response.)

CHAIR HEERINGA: I'll turn to Shalu Shelat or to Dr. Lowit, Jeff Dawson for any --

DR. LOWIT: I just have one thing.

I was listening to the discussion and envisioning in my head something akin to what I think Dr. Portier was talking about with respect to once we understand the translation between the Ag Health algorithm and the way that we do exposure assessment and on a distributional way that you can overlay the distributions and compare those.

And we certainly have experience -- - I'm thinking about the distributions of residential exposure. And we're really good at food. And we're really good at water. And compare those distributions and how far you incrementally get away from the Ag Health population.

Then the second step is what Dr. Gold very eloquently described with the extrapolation from a relatively homogeneous group to what is not across the country.

But what hasn't been talked about is the relative uncertainty of doing that compared to the default situation of starting

with an animal in the absence of let's say a pharmacokinetic model and dividing by ten. Or ten and ten. And the relative uncertainty of those.

CHAIR HEERINGA: Dr. Lu?

MEMBER LU: In my opinion, the uncertainty that Agency just mentioned is almost impossible to quantify because, again, this is really case-by-case situations. Say, for example, the methyl pyrithione misapplication case, for example, it involved quite a few people. We may be able to come up with an algorithm that you can calculate the uncertainty in terms of ag case versus the form it was illustrative.

But based on my experience of doing pesticide exposure research, there are many cases that -- you call them outlier but I think those cases are very important for the regulatory activity to examine the cause of the exposure and the manner of exposure and so on and so forth.

And I just don't see how can you generate something like this and try to come out with uncertainties so you can apply it to your approach. There are many risks that you will over estimate or under estimate the true exposures. And that would lead to a significant uncertainty as well.

MEMBER PORTIER: This is Ken Portier. Alex, when you mean case-by-case, are you thinking in terms of a scenario set to a scenario set? Or are you talking about an individual -- you know I keep thinking in terms of the way EPA looks at this in terms of, you know, a worker is really a set of scenarios that kind of get strung together. And then you are cumulating or integrating that exposure by looking at what they do during the day.

And I'm trying to figure out if you are thinking in terms of that or if you are thinking in terms of an individual, like an AHS individual who might be on the high end

of exposure with some kind of biomonitoring measurement.

MEMBER LU: Well, when I say -- what I meant by case-by-case is if you look at the distribution of pesticide exposure in say kids, you know, age three to five, if the Agency plans to use the Agricultural Health Study in a way that you can generalize for this population using some kind of a -- come out with the terminology right away, you actually tend to bring in those extremely high and extremely low exposure cases to the middle.

And that really dilutes the significance of this practice. And as I can recall, the principle of conducting cumulative research assessment for the pesticide within the Agency is to come out with some kind of a percentile. And then look at either the 90th percentile or above or 95th percentile or above.

By doing this generalization, that

95 or 97.5 percentile will become very flat and very similar to the 50th percentile. So that's the problem that I can foresee.

I'm not really talking about single case-by-case study like, you know, California cases versus North Carolina. But if you think about the much bigger picture, that's the case. You know bring everybody to the central tendency and you don't really see the cause and effect.

MEMBER REIF: That's a really interesting question and I'm fascinated. Has anyone ever done that for anything? For example, for benzene or for any of the industrial chemicals where you've actually taken the standard approach, you know, the no L and low L and the animal extrapolation in the ten then the ten? And then compared what you get for let's say a reference dose?

And then compared that with human data where there are really robust human data, which is not really the case here?

DR. LOWIT: I'm not necessarily really familiar with the benzene case but to my knowledge in the cases, with the exception of arsenic, the number we, or the Agency, has used an epidemiology study to drive a regulatory value, that has been done.

But how you interpret that has to do with the question that I asked about how you weigh the value, how you weigh those. I mean we spent several days and I've talked to many epidemiologists. And their first comment is always epi data is better than animal data because you don't have to extrapolate.

We only spent 30 minutes talking about I think very appropriate cautions of making -- going too far with the Ag Health Study but we're losing a little bit -- sight of, the default is a rat divided by ten and ten unless there is a PBPK model. And then, you know, you're still relying a lot on in vitro and everything else.

So the intellectual question I'm

asking myself is which is more uncertain? And their degrees of uncertainty.

CHAIR HEERINGA: I think the -- Steve Heeringa here -- let's try to break this down. When you go back to the extrapolation from the rat, you're really talking about dose response. And so I think there is a question about generalizability.

If a response was observed in the population of agricultural applicators, could we extrapolate that for equivalent exposures to their spouses and to their children? I mean that's one. In other words, can you extrapolate the mechanism?

I think what we're worried about is extrapolating the exposures. And I think -- at least that's what I'm catching. So I can't answer the question about the mechanisms. Somebody else might be able to.

But I think I would be inclined to be more comfortable if you, in the ag handlers epidemiologic study observe a response to

exposure that that mechanism might be more easily extrapolated than certainly information that you collect on the exposures themselves.

But, Dr. Reif?

MEMBER REIF: Yes, you're right. That's the answer you would get from an epidemiologist. But let me just point out one thing. Both IARC and EPA, in their definition of carcinogenicity, reserve the premier class or the Class I carcinogens to those chemicals that have adequate evidence of carcinogenicity in humans.

So both your Agency and IARC have taken the position that if you don't sufficient epidemiologic evidence of carcinogenicity in human populations, then you are a 2A or a 2B or wherever you come out in that framework.

So there's two independent bodies who have thought about this extensively. And their answer to that specific question is you must have epidemiologic data to classify the

chemical as a human carcinogen.

DR. LOWIT: Not being an expert on cancer classifications, in practice the Agency does cancer calculations on a number of chemicals that aren't in that first category based largely -- solely on animal data.

CHAIR HEERINGA: Dr. Bucher?

MEMBER BUCHER: I think I'd have to slightly disagree with that. I think that certainly the NTP categorizations and the IARC categorizations will rely on information from human studies but it doesn't have to necessarily be human epidemiology studies. It can be studies from humans in the sense of looking at similar mechanisms of action. And with respect to certain listings that we've made.

Certainly the epidemiology has not carried the day. It's been combinations of animal studies with other information that indicated that similar mechanisms occurred in humans. So it's not cut and dried.

I agree in general that epidemiology is considered needed to carry the day. But it's not exclusive.

CHAIR HEERINGA: Dr. Meek?

MEMBER MEEK: A couple of points. Fortunately we rarely have to exclusively use one or the other. So I, in fact, see the value of the framework as actually bringing the data together. And we need to distinguish qualitative considerations from quantitative considerations.

So the kinds of classification schemes that we're talking about that weigh epidemiological data do so -- or hazard characterizations, simply hazard identification has a characterization.

The kinds of information that we are generally seeking to do the risk characterization has to be dose response relationship data. So based on our experience in industrial chemicals, certainly there are some epidemiological datasets that provide us

with the dose response characterization that we need. And we use the data maximally.

And our experience there has been that the relative sensitivity of animals and humans isn't significantly different.

There are many, many issues embedded in the extent to which you weight the animal and the human data, some of which include, for example, if we talk about arsenic, you're talking about levels in the population that were tenfold above the kinds of guidance values that we're setting for drinking water.

I look at that data quite differently than if I have three or four orders of magnitude difference between an occupational population and a population exposed in a general environment. So there are a number of factors that are weighted.

The reason I made the comment the first day that clearly the qualitative considerations needed to be distinguished from

the quantitative considerations in this -- in the framework to use the data, we use the quantitative data as much as possible in epidemiology. We are rarely in the situation that we have sufficient quantitative data. So that's kind of where we've been.

CHAIR HEERINGA: Thank you, Dr. Meek.

Dr. Gold?

MEMBER GOLD: I'm fearing that I caused a problem here by putting in the cautionary note. So I'm going to put in as strong a cautionary note because I have the same concerns about extrapolating from animals to humans, namely that the modes of exposure, the applications, the routes of exposure, the dosages in animals are different. And the susceptibilities are different.

It's the same parallel I made between the AHS populations and other populations. So my cautionary note is the same.

CHAIR HEERINGA: Dr. Lowit?

DR. LOWIT: I think we've heard everything that we had hoped to hear, given that we didn't actually give you an example. It was in many ways an intellectual discussion of where to put our resources and how to think about it.

But I think it is actually the value of applying the mode of action framework under the context of the way that it has been used in the past and the way that we hope to put it here, is that by putting everything down, and all those uncertainties whether they are the cautions that Dr. Gold talked about and the similarities of what we know about the pharmacokinetics of animals and humans that by building that case in a stepwise, very transparent way, that those -- that that weighting becomes apparent as you go through the analysis.

The reason I asked the intellectual question was because I was

getting this very negative vibe and I wanted, as a group, I wanted you to step back and come back to our reality of that the alternative is if you come out a little too strong on, you know, nothing other than applicators, that's a challenge because the default is something that most people find fairly dissatisfying.

CHAIR HEERINGA: I won't speak for the group but I think that won't get precisely that message. It will be a more diffuse message, appropriate with a question, I think.

Other comments on this last point?

(No response.)

CHAIR HEERINGA: Okay. What I'd like to do is to go around the panel and give everybody an opportunity to sort of address anything that you think has not been addressed relevant to this particular topic that we've been discussing for the last two-and-a-half days. Something that relates to one of the charge questions you haven't mentioned. But anything you'd like to offer.

Let's start with Alex, Dr. Lu?

MEMBER LU: No, I have nothing to add.

CHAIR HEERINGA: Dr. Hayton?

DR. HAYTON: No, nothing further to add.

CHAIR HEERINGA: Dr. Reed please?

MEMBER REED: I don't really have anything to add into this -- the context of the questions. But I do have a risk assessors sort of same point. When we talk about human data being more desirable in terms of having advantages, in the context of pesticide risk assessment, it is a little bit unsettling to me because I've always thought that if we do risk assessment correctly, then you wouldn't see any of these human data in terms of illnesses and all that.

And so when we put it out as wow, you know, human data is much better advantage over the animal data, I'm hoping or wishing that there is a way to express it in a way so

that it is not conveyed as we're looking for that human data to make risk assessments better because there is a component of risk assessment which is predictive. And human data observation in populations and incidences of illnesses is not predictive.

And so I don't know how to, you know, put it in a sentence like that but I think something like that would be a useful conversation or communication.

CHAIR HEERINGA: Dr. Reif?

MEMBER REIF: I just want to really commend the Agency for taking us on. You go back to the original description, at least from my recollection of the NRC's monograph in whenever it was -- 1983 -- and think about the number of years that have elapsed where we really haven't successfully and adequately, in my view, integrated epidemiology into the risk assessment process.

This is a real challenge. And it isn't easy by any means. But I think that the

fact that you are clearly interested and committed to seeing how and to what extent it can happen and it can work and consider it is a huge step forward. So I just think it is very worthwhile.

CHAIR HEERINGA: Dr. LeBlanc?

MEMBER LeBLANC: I have nothing to add.

CHAIR HEERINGA: Dr. Portier?

MEMBER PORTIER: One of the things that has been in the back of my mind through all of this discussion is how we used a lot of the human data in the CCA risk assessment by passing it through some kind of a model. And I haven't seen any kind of conceptual model.

And I think, you know, while the conceptual framework that you've had is nice for thinking about these things, it's almost like a lot of these questions could have been answered if we had had a more concrete model about how you are looking at how these, you know, exposures occur and everything else.

So I would encourage the Agency to continue to think in terms of how we use the scenarios and modeling to actually compare to the epi data and use the epi data as more of validation that our understanding of this process is clear and logical.

MEMBER CHAMBERS: I don't have much to add but I think Ruby just brings up a very interesting point. If the risk assessments have been done right up to this point, then you might not get any positive adverse -- or any adverse effects out of the human study and you will have to revert to the defaults to look at what the adverse effects might be in an animal system.

So, anyway, good luck.

(Laughter.)

MEMBER BUCHER: Well, picking up on that also, if, in fact, the Agency does find with the review of atrazine or any other pesticide with significant human data that there are significant human risks that are

associated with the use of these pesticides, I think one needs to go back and reassess the entire paradigm that you are using to protect the public. And maybe readjust some of the safety factors that are in use and some of the assessment techniques because obviously that would represent a failure of current practices.

So it is a very important thing that you are doing here and I encourage -- even though there has been some tendency toward some critical comments towards the Agency's approach, I certainly do encourage you to go forward with this because this is very, very important.

MEMBER POPE: I'd start just by saying that I think -- I appreciate the idea or the concept of using any kind of data to input into the risk assessment process. But I am an animal toxicologist so I have biases just like epidemiologists and other people in different disciplines.

And Dr. Meek just mentioned something about when you have the situation where you've got really widespread differences in apparent dose response relationships, for example between epidemiological studies and animal studies, and I also, like Ken, have been sitting here for the last couple of days mulling over something and it's what Dr. Lu had just brought up about the 2008 SAP meeting on chlorpyrifos.

And my recollection from that was that animal studies and epidemiological studies were both kind of a suggestion that there were neurodevelopmental effects that were being listed by chlorpyrifos early exposures or possibly chlorpyrifos and other OPs.

But the distinction was that in the human studies, the doses appeared to be incredibly much lower than the animal studies were. And so I've been sitting here trying to figure out how do you epidemiological data

versus animal data under those conditions?

And on page 31 of the white paper, there are a couple of points there that say when animal and epidemiological data do not provide a consistent toxicological picture, more weight would likely be given to those studies with robust study design and availability of replication or confirmatory data.

Robust seems like a good term for definition. Further it assets that in most situations, the epidemiological study may not be sufficiently robust for deriving quantitative risk assessment values. And as an animal person, I think I agree with that.

And that animal studies have a better chance of more quote robustly describing dose response relationships and mode of actions than epidemiological data would be able to do. And I'm wondering, you know, what the epidemiologists think about this.

CHAIR HEERINGA: Dr. Bailar?

MEMBER BAILAR: I'd like to echo Dr. Reif in commending the Agency on taking on a very difficult problem but one that I think is necessary. I'd like to go further and commend them on what I think is a very sound first draft.

It's the very quality of this draft that has made it possible for us to address the questions that the Agency has put to us. Also, it's really a lot more fun to try to make a good thing even better than to make a lousy document just marginally acceptable.

CHAIR HEERINGA: Dr. Meek?

MEMBER MEEK: A couple comments along the same lines. First of all I very much appreciate the efforts of the Agency. And having been on the other side of the table for Health Canada many times, I understand what you go through in these review processes. And I hope that you come away with something

very helpful in the discussions.

I would encourage the Agency to think not only in the context of epidemiological or human incident data in the context of human data as we transition to think more broadly about the kinds of, you know, early events that we'd be looking at in populations.

And I really think that our, you know, our context of epidemiological studies is going to need to change as well. So rather than considering epidemiological studies as our having failed in some context because we're counting very adverse effects, we probably need to be thinking about how do we look at biomarkers that can more robustly inform us in the context of mode of action.

MEMBER GREENWOOD: I think having sort of listened through the presentations by various people and having listened to the discussions over the last few days, I guess really for me the way that the Agency started

to approach this, using a series of frameworks, I think is probably a very, very good way to deal with this.

I mean I think actually I would encourage them to provide frameworks which look at all of the individual stages so that you have a framework for setting toxicological data, epidemiological data, the exposure, and so on. So on all of the designs, that you have something which is transparent, which is the sort of thing you are working to across the board.

And I think maybe you need to look in more detail in some areas where it is critical to try and develop a step of criteria by which you assess the validity so you can apply it to any of the studies in exactly the same transparent way.

And certainly I think what I see happening where you are beginning to bring different disciplines together is really something which will help you achieve what

really otherwise would be, I think, a very, very difficult job.

But I think the approach, using a series of frameworks you've started on, is probably going to allow you to make -- have a lot of success in looking at what are some very difficult problems.

MEMBER HARRIS: Well, I don't think I can add much more that hasn't already been said. But as someone who was trained in toxicology and exposure assessments and, you know, I jumped camp over to epidemiology and I did that because of my absolute frustrations of looking at the exposure assessments in the pesticide exposure health risk studies.

And then after many years of working in that field of epidemiology, I realize that yes, it is very difficult. And we haven't gotten much better at doing it.

So I might just reemphasize that the need to really expand work in the exposure assessment as it relates to both. And I thank

you for being here because it has been quite a pleasure trying to wear two hats. I don't know if I've done that effectively or not but I will continue to try to do that for many years.

Thank you.

CHAIR HEERINGA: Dr. Bove?

MEMBER BOVE: I just want to echo what a number of people have said. I think it is just great that you are moving in this direction. And go forth.

CHAIR HEERINGA: I'd like to express my thanks to all of the members of the panel and to the scientific staff of the EPA. I would especially like to thank some of the younger scientists who have made presentations here over the last three days. I can only imagine that it is challenging and you are being thrown into the lion's den of sorts here.

Because the purpose of this is to critique. And so the criticism comes more

easily than the praise. But I think you just heard a fair amount of praise here as well, too.

And I think that you should be commended for I think the quality of your work and the clarity of -- I don't know many first drafts that I've written that would have had that sort of clarity.

And following Dr. Bailar's comments, we were able to follow it and we were able to consider it and comment on it. So it's very effective. And hopefully you'll take any "criticism" not personally but as part of the scientific process of getting to where you want to get to.

I thank you also to all of our public commenters for the information that was shared. I agree with the other panel members that this is an important deliberation. I think it was an important deliberation to have at the start of what is going to be a very year for this Science Advisory Panel, some

very, very serious deliberations. I hope that the sessions that we've had here the last two-and-a-half days will essentially inform us and inform the EPA in the process that we are about to go through in this coming year.

So any additional comments or suggestions? Dr. Lowit?

DR. LOWIT: We would just like to take a second and thank each one of you. Your participation in this process is absolutely vital to our everyday work of making sure our assessments are scientifically robust and transparent. And pushing and prodding us to do better and better.

And I'd also like to thank Myrta Christian and Laura Bailey who have once again put together a stupendous meeting. Everything runs smoothly in the background, which is wonderful.

And I'd also like to thank my team. It's a small army of people you've seen and some that you haven't.

CHAIR HEERINGA: Thank you.

I'd like to turn it over to Dr. Myrta Christian, our Designated Federal Official.

MS. CHRISTIAN: Yes, I'd just want to thank you the panel for their advice to the Agency, the public commenters for presenting their views to the panel, and especially the Agency for their excellent presentations.

And in addition, I want to remind everyone that the report and meeting minutes for this meeting will be available in about 90 days.

CHAIR HEERINGA: Okay. With that, I'd like to again thank all of you for your participation. And we will bring this meeting to a close.

Panel members, let's meet next door to plan the afternoon's writing sessions.

(Whereupon, the above-entitled Scientific Advisory Panel meeting was concluded at 11:22 a.m.)

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