FIFRA SCIENTIFIC ADVISORY PANEL (SAP)

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DR. ROBERTS: Ms. Olga Odiott, our designated federal official has an announcement.

MS. ODIOTT: We have received several requests for the availability of the agency presentations and the overheads that have been given to the panel.

We are making extra copies right now, and we're putting those copies in the docket. They should be available from the docket by Monday.

In addition, we have the electronic copies of these presentations and the overheads. And they are already with the person who posts all this information to the web site. They should be available tomorrow morning.

So I hope that satisfies the request of many people here that are very interested in having these copies.

DR. ROBERTS: Thank you.

Dr. Doyle, Mr. Miller, would you pose the first question to the panel, please?

DR. MILLER: There are several key principles for conducting a cumulative risk.

One such principle concerns the time frame of both the exposure, what is the exposure duration, and of the toxic effect, what

are the times to peak effect and the time to recovery.

Both must be adequately characterized prior to performing a cumulative risk assessment so that an individual's exposure is matched with relevant toxicological values in terms of duration. There are several important considerations with respect to the temporal characteristics of the exposures and of the cholinesterase inhibitory effects of organophosphorus pesticides in estimating their cumulative risk.

There may be single day spike or short term exposures to organophosphorus pesticides via food, nonoccupational residential uses and drinking water as well as more or less continuous exposure via the diet, food.

In the preliminary OP cumulative risk assessment, OPP used relative potency factors and points of departure developed from cholinesterase inhibition in rats exposed to pesticides for 21 days or more.

This practice was adopted to reflect cholinesterase inhibition at a point in the treatment schedule at which a steady state had been achieved.

OPP elected to use data reflecting a steady state in the interest of producing relative potency factors, RPFs, that are reproducible and

reflect less uncertainty due to rapidly changing time sensitive measures of cholinesterase.

In addition, when the compounds are at steady state, the differences in toxicokinetics among the OPs are less likely to impact the assessment.

OPP has information that indicates that the American population in general has some continuous level of exposure to OPs. Biomonitoring data from NHANES suggests that more than 80 percent of the American public have urinary metabolites indicating possible exposure to OPs.

Most animal data available to OPP are developed using laboratory animals that were not previously exposed to OPs. In other words, the laboratory animals used in the toxicology studies were naive in their exposure to OPs.

These studies show that OPs can produce cholinesterase inhibition after a single exposure. A rough comparison of the BMD10s derived from female brain rat cholinesterase data from 21 days or longer duration with no observed adverse effect levels based on cholinesterase data from single dose studies reveals good similarity of values with differences rarely exceeding two to threefold.

Also, animal data suggests that recovery from a single exposure

may take days to weeks.

In light of all these factors, OPP wants to evaluate exposure across the most appropriate time frames.

In the preliminary OP cumulative risk assessment, OPP developed a distribution of single consecutive day exposures considering the pattern of margins of exposures occurring at a particular percentile of exposure across the calendar year.

This approach focuses on exposure to the population of interest as a whole rather than attempting to track the variation in an individual's exposure from various sources of pesticide exposure.

As an example at the 95th percentile of exposure, each day of the year will reflect a 95th percentile exposure for the entire population and not reflect what may be lower multiday average exposures for any given individual.

Calendex allows calculation of multi-day, rolling averages of exposure estimates for the individuals within the population. While this may allow for a match between selected exposure time frames, for example, seven days or longer, and the hazard endpoint, OPP is concerned that this may not adequately permit estimates of risk associated with shorter duration exposures.

The question to the panel is, please comment on how best to

evaluate risk taking into account the temporal characteristics of the hazard endpoint, that is, cholinesterase inhibition, and the temporal characteristics of the exposure patterns for the food, drinking water, and residential/nonoccupational pathways, with specific reference to: The pros and cons of various approaches of combining the exposure and hazard time frames to estimate cumulative risk, and methods to estimate the biases in each approach.

DR. ROBERTS: Thank you. A challenging issue.

Before we get to the responses, again, let me please ask the panel members to focus their comments on the response to this particular issue, and then we'll have opportunity for other comments on other even perhaps related issues later on.

Dr. Rhomberg is scheduled to lead off our discussion on this. Please do so.

DR. RHOMBERG: Thank you.

Well, first of all, I would like to thank the OPP for a very clear explanation both yesterday and today of the nature of these issues. And I think that that is going to help a lot in our discussion. It was very well laid out.

I think it was helpful the talk this morning about the nature of the problems that was maybe expanded maybe even a little beyond

what was in the document. And I think that some of the problems that the agency sees are little bit clearer after this morning's explanation, at least they are to me. And I think that they have noted some real issues.

If I may, I'm going to have a little bit of a long answer, because I think that the issue here is being confused by two separate things being muddled together.

And I think that spending some time structuring the issue is probably worthwhile for the benefit of the discussion of all of us. So I'm going to go on for a little while, but I don't mean to be dominating. But I think it might be helpful if I'm sort of able to work through my answer first.

And I would like to also just as a preface say that it is really important here to distinguish between the ideal and the possible.

And I think it is worthwhile discussing both of those. We discussed the ideal not because you didn't do it and it is not right until you did, but rather you have to really know where you are trying to head with this in order to decide how far you actually have gotten already and are able to get with practical measures.

So I think it is worthwhile talking about both of those issues. But I am really going to try to be practical.

Obviously, the practical constraints are data. When you start thinking about sophisticated things, they usually require data. Time, in that you have a quick schedule and you have been working on this for a while and you would like to get finished and I think people would like to see it done.

And frankly, also, there is an issue of familiarity and policy issues. When you try to do different things, it takes a while for everyone to be comfortable with the fact that, yes, this really means what it appears to mean and it accomplishes what we want it to accomplish and we're not fooling ourselves.

And frankly, I think that that might be something that might become limiting here just because there are some more things to consider here that haven't quite been touched on.

What we're faced with here now is the longitudinal exposure profiles that you can get for individuals from the Calendex process as described before.

If this is an ideal thing, if we say this is really done well, then it reflects people's patterns of exposure over consecutive days in a way that we can rely on.

I think it is probably worthwhile separating the issue of have the existing profiles that you have been able to calculate so far with the

methods you have on board achieved that.

In other words, do we have good profiles that we can rely on from the question of given good profiles how would we use them and how would we interpret them.

And we spend a lot of time -- in fact, one of the questions yesterday was really about how good are the profiles in the ways of getting for them for longitudinal exposures characterization.

I think it is fair to say that there was sort of a mixed reaction on the panel to how sort of, well, we think that has been achievable so far.

Some of the comments today, including the public comments, are really about that former question, I think of, you know, are the profiles any good.

We can reopen that if we think we need to, but frankly, what I'm going to do in my comments is assume we have profiles that we think are good or good enough to use and focus on the question of how do we use them and how do we interpret them.

Well, certainly, when you can do this you've got several advantages that handles the issue of multi-day exposure patterns and the possible positive correlation, the leftover effects and things like that.

It allows for ongoing effects like the gradual attenuation of exposures that come from a residential exposure or something like that as we heard about earlier.

And nonetheless, most exposures are not going to be of the sustained type. And it will allow for the fact that when you average in some high peaks and some lower things, things like that, the averages are lower. And that's important to understand as well.

So the question is if we have these, how do we use them.

Well, since -- as I say, I am going to go on for a little while. I think I will quickly sort of state the main idea, which is, I think that there are two issues that you would want to talk about with some sort of averaging kind of process.

And that a lot of the difficulty that you are having with it stems from not really distinguishing those and recognizing them as two separate things that maybe even need sort of two separate averaging exercises.

The two things are, basically, pharmacokinetics and pharmacodynamics. On the one hand, the relationship with exposures and the history of exposures to the changing pattern of cholinesterase's inhibition day by day that will change as a function of current exposure and exposures in at least somewhat recent past.

That's on the one hand.

Clearly, that involves some longitudinal issues of exposure there.

And then the other one is a toxicological issue of given that you have a profile like this of changing cholinesterase inhibition, how long can you tolerate various degrees of cholinesterase inhibition without having a toxic effect.

Maybe you can tolerate a very severe inhibition for a short time and not as -- maybe a lesser inhibition if prolonged for a long time would also cause some concern.

And obviously, both of those issues are on the table. And as I say, I think the part of the problem is trying to address both of them with one rolling average approach when in fact there are two things.

So let's look at that first issue, the one I have called pharmacokinetics.

I'm going to start by just sort of considering the way toxicological testing is done and the way doses are expressed and how those would relate to cholinesterase inhibition.

First of all, consider an isolated single dose experiment. When I say isolated, I mean in a naive animal. You give them a single dose as quickly as you can and see if it's enough to cause acute toxicity.

If you give larger and larger and larger doses, you will get higher and higher peak levels of cholinesterase inhibition.

And in that situation where there is no previous exposure and failing to have some sort of pharmacokinetic difficulties like saturation or metabolism or whatever like that that for the time being let's set aside, assuming the pharmacokinetics are straightforward, the dose level that you give in that single dose is really a surrogate for the peak concentration that you get. And they will be linear related and you will double the dose and you will pretty much about double the peak concentration that you achieve. And so you can use one as a surrogate for the other.

But, of course, we don't have that because we have ongoing other exposures that will have occurred before the peak. And so we want to say, how do we deal with that when we don't have that.

Let's think of the other kind of testing. Chronic toxicity testing where you've given exposure for at least -- it doesn't have to strictly be chronic in the strict sense of the word, but at least ongoing exposures of the kinds that were used in the relative potency factor exercise.

Here you have, again, starting from zero, but you have a dose rate now that has continued on for a period of time until you achieve

steady state.

Here again, the dose rate, the number of milligrams per kilogram per day that you use eventually has a one to one correspondence in its linear relationship with a steady state concentration of or steady state level of cholinesterase inhibition that you achieve.

So again, in the strict sort of paradigm toxicity testing where the things are kept simple because of experimental reasons, you have this nice correspondence. And the dose rate is a surrogate for the cholinesterase inhibition level that you achieve.

But we don't have that either in this situation. We do have ongoing exposures, but they are not constant, and so they won't come to a steady state. They will pop up and down. They will go up and down depending on the changes in the dose rate from time to time. And so we have to figure out how to deal with that.

Now, traditionally, in risk assessment what we have done is hope that these two alternatives that we have that we do by different kinds of testing and that we evaluate different kinds of exposure scenarios by, when we do a risk assessment, sort of more or less correspond.

We say, well, if typically speaking background exposures are so

low that the spike that we get from an acute exposure is essentially like somebody was naive, then the testing in the naive animals is directly relevant.

Similarly speaking we say on chronic exposures if it's sort of more or less an ongoing exposure of the same kind of level, then that will tie in humans to a sort of steady state level of whatever the thing is being caused, the concentration of the compound or the effect it may have or, in this case, cholinesterase inhibition. And again, the animal experiences directly relevant setting aside all of the problems that we always have with cross pieces extrapolation and so on. But it is sort of qualitatively relevant the kind of thing.

So then the question is what do we do when we don't have that. We have this fluctuating thing. Let's go back to the acute case again, this single spike exposure. But now say, okay, this happens in the context as Dr. Doyle was showing some ongoing exposure that you had before and not in a naive animal or naive person.

Well, the one day exposure you have, you really can't just take that one day exposure and compare it to an acute level because you are starting off, as was explained this morning, from some background level of cholinesterase inhibition that comes from your previous day's exposure.

So if I see how high I can jump off the floor here, I can jump a certain height. But if I stand on the chair and jump, I will reach higher. And it is not me who is jumping better. It is that I'm starting from a different level.

So what is the chair here? What is the chair? The chair comes from previous exposures on previous days.

So when you think about this now from the point of view of the rolling average, clearly a rolling average that is centered the around the day can't be doing it. Because how can exposures that you are going to have, now for an acute toxicity issue we're talking about, how can exposures you are going to have tomorrow or the day after or something like that affect your level of peak cholinesterase inhibition that you have today.

I will gladly expose you Tuesday for a toxic effect today. It doesn't make sense.

So at the very least, for an acute exposure or for this sort of pharmacokinetics issue, you have to go backwards in time and not the other way, not forwards, when you are doing a rolling average.

But beyond that -- then the question is how far back do you go. Well, beyond that, it is clear that if you go back far enough, the exposures that you got a month ago, two months ago, those are no

longer affecting your background level of cholinesterase inhibition today.

What happens in an execute exposure is you get a peak of inhibition and then you get a gradual decline in that as you recover from it. That decline can be rather slow.

But it happens at a nice exponential rate at least in simple kinetics.

So what you can really say is that the cholinesterase inhibition level that you have today from today's exposure is a product of today's exposure, plus some fraction of yesterday's exposure that is sort of hanging over and causing some residual uncorrected, unrecovered inhibition that happened yesterday.

Plus, some smaller fraction of the day before that, and some maybe smaller fraction still of the day before that and so on.

So what you really have is instead of -- first of all, the weighted average has to go backwards in time. Secondly, it shouldn't weight every day equally. It should weight the current, the most recent days more than the more distant days.

How specifically could you do that. Well, you could really do that with sort of an exponential decay type of thing where you say, why is there this kind of exponential -- why is there an exponential

return from a peak level of inhibition back to normal.

Well, you, I don't know, clear the compound out and/or you repair the cholinesterase that has been affected and/or you synthesize new cholinesterase. So all those processes are going on. You eventually recover.

So I think if you see it this way, you realize that at least one reason for the rolling average thing is to try to be a, sort of, account for this pharmacokinetic kind of process. Because that's what this is. It is pharmacokinetics. Older exposures have less effect on your current level, but they all back to sort of several half lives and in the past have some effect.

And how would you then handle this other than by a rolling average. Well, certainly, as I say, it should go backwards. It should sort of diminish the further out it goes.

One possibility, which Dale Hattis basically, accidentally, adumbrated my remarks with, was to do a simple pharmacokinetic model of the kind that Woody Setzer did in the relative potency factor curve fitting exercise. It showed the power of a simple model like that.

And basically, this one would have to be maybe even a little simpler than that. And you could find a way, then, of tying an amount

of exposure with the cholinesterase inhibition causes today and the next day and the next day and the next day and so on as a way of doing this kind of averaging.

Or even simpler than that, a suggestion that I actually made a number of years ago, and, frankly, most of my comments today are going to be trying to remember what I wrote on this issue about three or four years ago at the Vermont Elsey (ph) Aggregate Risk Assessment Meeting, where this issue at least -- well, that was sort of the beginning, if I may, sort of, crow for a second, it was at the beginning of the consideration of models like the life line model where you were starting to actually look at calendar-based approaches.

And I, at least, recognized then that some day we are going to be at exactly the point we are at today where we have to decide how to interpret toxicologically these results, and what would you do once you got there.

This is before we could do those things. I said, one of these days we are going to succeed. I was convinced we were. And now, we have. What would you do with those results.

I wrote a little essay about how you would do it. Basically, I'm repeating that now.

What did I propose, then? To use basically a half life of

recovery from the sort of peak of cholinesterase inhibition as a way to decide how that exponential weighting should go off into the past.

So for instance, I'm going to make it simple and say let's say a half life is a day. And I know that's too short for real. But let's just say that it's a day.

That means that you would count today's exposure fully, half of yesterday's exposure, plus a fourth of the day before's, plus an eighth of the day before that.

And pretty soon it goes away to zero. So you really only have to go out five or six days. The longer the half life is, the longer back you would have to go.

Please note this is not averaging those. It's actually summing them up. Because that four days ago exposure still is affecting your sort of, you know, the chair that you are standing on to some degree, although in a diminished way the farther away you get from it in time.

That would be very simple to do. You just sort of apply this sort of running sum, exponentially weighted running sum and then go through. Instead of a moving average. It is in simple enough calculation that I did it on a spreadsheet there to make a seminar in a half an hour after I thought of it.

So it is not hard to do computationally.

How do you get that factor, that half life factor? We say, oh, we have to go find this in the literature and so on.

I think you actually have gone a long ways towards that already in the analysis that you did of the steady state data, how long do you have to go to get the steady state. Because the time it takes to get to steady state is also directly related to this half life.

It is sort of delimiting half life. It's the half life that sort of limits -- of the process that limits the recovery rate. And as I say, that might be resynthesis of enzyme. It might be recovery of enzyme. It might be clearance of the compound depending on the thing. It could even be different for different compounds in a way that would be interesting to take into account.

Basically, how long does it take to get to steady state with a repeated dosing thing. About four half lifes. Four or five. Depends on how clearly you think you've -- you know, the exact point of where you think you have got steady state. Obvious -- mathematically, it is infinite time because it's an asymptote. But you get very close within four half lifes essentially at steady state.

So you could say, okay, 21 days. So a fourth of 21 days. That's about five days is a half life for these. Obviously, it is shorter for some and longer for other compounds.

Frankly, I think the difference between compounds won't be such a big deal here compared to -- the bigger factor would be just what do you choose for the sort of central estimate of all this. You could probably do it with one half life. Or if you think you have the data for it with several compound specific half lives.

Now, this is all practical. Obviously, the ideal thing to do would be a real pharmacokinetic model. Before Rory says it, I will say it. A real pharmacokinetic model where you can look at the metabolic activation and the clearance and any kind of interactions and saturations of processes that go on there and so on and so forth.

That kind of modeling is probably accessible, but not quite in the time frame that you have here.

On the other hand, this simple thing or probably the pharmacokinetic model as Dale was and probably will again suggest, is probably something you can do in your time frame.

I would also say something you should do from this point of view. It is not really addressed in the document what kind of level of cholinesterase inhibition you would expect in humans given dose rate and milligrams per kilogram per day vis-a-vis what you saw in the rats.

I think it is sort of implicitly assumed that it should be the same. But it is almost surely not so, because half lives tend to be

longer in humans for various reasons. We have slower physiological processes. It takes us longer to pass all of our volume of distribution through the expletory organs. Metabolic rates are slower. And things like synthesis of protein also tend to be slower too.

How much slower? A good guess would be based on allometric scaling by the one fourth power of body weight ratio that, again, Dale Hattis mentioned. This is sort of physiological time scaling. Roughly speaking, human bodies run sort of four times slower than rat bodies.

And so you would say maybe four times longer. That would make a 20 day half life in humans.

You really have to somehow somewhere take that into account. Because if you don't, you are not allowing for the fact that five days ago exposure in a rat they have had more time in terms of clearance activity to get rid of it than a human would, because a human clears it away more slowly.

For every other kind of compound with this kind of slower clearance in humans, the result that is for a given milligram per kilogram per day rate the concentration at steady state goes higher or in this case the amount of enzyme inhibition would be higher.

Again, by about that factor four. So if you don't take that into account, I think you are missing something important.

If you did the kind of calculation I was talking about, it would automatically take this into account, because you would need to use the half life, obviously not of rats, but of humans in doing this kind of, what I was calling it, exponentially weighted sliding or progressive sum or something like that, I can think of an another name for it, that would automatically take into account.

Parenthetically, if you did this with different half lifes for the different compounds, you could do that. And if they're radically different, it could make a big difference.

This, frankly, is an automated answer to a question. If you don't see it looming on your horizon, you probably should. Carbamoates (ph) and OPs. Carbamoates have much shorter half lifes. There is the famous phenomenon of the carbamoate comes first, then the OP comes second. And then you just switch the order, but with the same doses, and toxicity is completely different.

Why is that? It is because one of them lasts longer in the body. It just raised the chair for the other one more, so to speak.

That would be automatically taken into account by this half life issue.

It would be, I think, a good way of handling that issue. In fact, the only way of handling that issue.

It also emphasizes that in this whole process what we're really doing is we're making an assessment of carboxy -- sorry of cholinesterase inhibition.

This is an interesting thing about the whole cumulative risk problem, which is, in a way, a little bit of a tangent here that I didn't want to get off to.

But when you do a common mechanism of action based assessment, you are really making the assessment of the mechanism of action in the various ways of sort of affecting it.

And the class of compounds that all do that is in a way almost sort of an arbitrary thing. So we're really making an assessment here of cholinesterase inhibition as affected by a whole set of compounds.

Putting all this stuff in terms of cholinesterase inhibition then makes it into the common currency that's really sort of implicit in your whole approach to the thing, or inherent in the whole approach to the thing.

So what would happen if you did that kind of weighting that I was talking about. First of all, you have to realize it's a different kind of exposure measure because it is not sort of a daily exposure and it is not an average daily exposure. It's this sort of summed up thing.

So the numbers will get big because you are adding exposures

from previous days, although fractions of exposures from previous days.

You have to tie that to the cholinesterase inhibition that would result from it.

And the way you do that is by doing the same kind of exponential process on the rat data that you use for the steady date and say, this kind of steady state, exponentially weight exposure thing leads to 10 percent. It is just a matter of rescaling the dose scale, and that will all take care of it. So that should not be a concern there.

What does that all mean for all of this? That, clearly, one of the reasons for doing this kind of moving average is really sort of a poor man's pharmacokinetics. And it doesn't work for that.

On the other hand, a small modification of it would work pretty well.

What I just described probably gets 80 percent of what full pharmacokinetics would get you, I would say. Rory is not quite so sure.

I don't think that in the long run -- I think in the long run you want to try to do the full blown pharmacokinetics. But I sort of predict -- I know that in the short run you won't be able to do that. And I predict that in the long run when you do the answer you get

from this will be quite close to that.

So that means you have to do, even for acute exposure, just for the peak, you still have to do this kind -- some kind of rolling average but modify the way I have discussed in order to really get the right answers.

Now, what about the other issue? That other issue still exists. That other issue of, well, okay, so for acute exposures, the issue is peak inhibition rate -- or for acute toxicity, I should say. It really should say, for acute toxicity, the issue is the peak that you achieve.

You could assess that easily in these profiles by doing the kind of thing I get. I basically would recommend translating all this into an estimate of the degree of cholinesterase inhibition you get. This common currency that it's really all based on rather than leaving it in milligrams per kilogram per day and having the MOE in that same unit, sorry, the BMD in that same unit and judging the MOE in terms of cholinesterase inhibition.

And you could run through your profiles and see if there is ever a case where exposures sort of build up in their pattern in a way that will ever throw you up over the top.

The image that you could have is these little VU meters that you get on stereos that bounce up and down with the music.

And then the question is, does, in the course of a whole song, does it ever get over into the yellow or the red zone or whatever. That's for acute.

But you say, okay, it is also conceivable that a prolonged exposure to inhibited cholinesterase at some lesser level than this peak that would cause toxicity nonetheless could have toxic effects. Maybe 20 percent inhibition for a week could have -- I'm just pulling that out of the air, I don't really know this from any data, could cause an affect.

Or maybe it is 15 percent inhibition for a year or whatever.

Basically, other ongoing toxicities would then have to be evaluated in terms of how long you can tolerate how much inhibition. And the difficulty there is that our experiments are always done from this sort of naive animal steady state dosing thing so that we can make that kind of easy connection between the dose rate and the steady state inhibition that sort of allows us to operate in the realm of -- the familiar realm of sort of external exposures rather than internal measures of dose.

When this fluctuating around like that, you can't do that anymore. It doesn't work. And so what you would then have to do is say we have the same profile now operated on by this smoothing and

integrating process of the exponential thing to get cholinesterase inhibition.

And you could now again do a second run through it. This time really doing weighting average, running weighted average. And say, okay, if you have going through on a seven day scale, if you ever get above a certain level on the seven day weighted average thing, then you run the risk of toxic effects that happen when you are over that level for that amount of time.

And if you do with it a 14-day weighted average, you run the risks of things that would happen if you stay above that level for that amount of time.

The challenge, then, is a toxicological one of turning our studies of toxicology in a way we express doses in them into the kinds of things that could say this sort amount of time spent above level X is what is actually causing the toxicity and things that don't make it that high or for long enough don't keep the inhibition high enough for long enough would not have those effects.

That's a challenge to figure out how to express the toxicity that way. But in a way, you are sort of stuck with it. You have to sort of figure out what to do.

Again, to make it practical, though, what you could do is you

could do lots of different averaging times. And you will probably discover and the way the data looked to me, you will probably discover that averaging times over a certain amount of time, running averages, once you do it on this inhibition -- translated into inhibition levels data will probably be, you know, have acceptable margins of exposure.

And if it is acceptable for a certain averaging time, it will be acceptable for all longer times than that.

Because, for instance, the way you seem to be interpreting the data on the 10 percent inhibition in the rats is, okay, it takes 21 days to get to steady state, but the implication is that longer and longer times the inhibition doesn't get any worse and neither does it cause any toxicities, that you could tolerate 10 percent inhibition indefinitely.

So that means that any averaging time that keeps it so that you never have 10 percent inhibition, anything longer than that is going to be even less of a concern. And you can sort of see how long the time has to be in order to get yourself into that ballpark and see what -- does that make sense that you are avoiding those toxic effects from what you know from the toxicology.

So that's a long-winded way of saying that I think there are two issues. One is a pharmacokinetic one, which you could solve

perfectly with pharmacokinetics, but you can solve probably very close approximately with a modified kind of weighted average of the kind that I was talking about allowing for cross pieces extrapolation of the half time issue.

And then there is a second issue which is the toxicological consequences of the profile of day-by-day cholinesterase inhibition that you got out of the first step, and go through that again with a bunch of different weighted averages and see sort of how long you have to stay over what in order to, you know, sort of get something that looks high compared to what you see in toxicological studies and the kinds of internal exposures of enzyme inhibition -- of a cholinesterase inhibition that led to toxicity in those experiments.

I think that if you do that, again, this is all predicated on the notion that these profiles of the exposures you get are good enough to handle all of this, you really sort of bracket things. On the one hand, you have the acute effects. On the other hand you have sort of, say, chronic and anything longer than this is also okay.

I think that you can probably with the data you have, but just a little different way of treating it and analyzing it at the end, come up with a fairly good characterization of what is going on.

But it comes by separating those two issues and realizing that

you can't do them both with one averaging, one rolling average. You have to do it twice. One for pharmacokinetics in the special way that I mentioned and then the other for toxicity.

That was long enough. That's about it. I guess I will let everybody else comment on this and their perspectives as well.

DR. ROBERTS: Thank you, Dr. Rhomberg.

Actually, you posed some interesting ideas. Before we get to the next comment, I wanted to check with the agency. Do you want any clarification on his comments before we move on, or would you want to sort of hold those until you hear from other members of the panel?

DR. DOYLE: I think for our purposes, and if you disagree, tell me, but I think it would be nice to hear a range of comments and then have a discussion if that would be all right?

DR. ROBERTS: That's absolutely fine. Let's go, then, to Dr. Brimijoin.

DR. BRIMIJOIN: In comparison to Dr. Rhomberg, I'm just a simple pharmacologist. I feel like something like a guy who spent most of his life trying to predict the weather from cloud formations, humidity, temperature, dew point, and now we're entering the era for four dimensional climate modeling on a super computer. So I'm not

going to attempt to fly the super computer.

So I agree totally with Dr. Rhomberg's approach in general as an ideal to the extent that I understand it.

So I'm going to raise -- I think we have heard about a way which -- I think you have done a nice job of pointing out something short of the ultimate ideal of a perfect physiologically-based pharmacokinetic model, which would nonetheless capture a great deal more of the actual variation that is going to be out there and the toxilogical consequences of that. And I think that's commendable.

I'm somewhat uncertain about whether in the time frame that we're talking about now whether -- how well EPA will be able to rise even to that next level. I guess I would see that as possibly the next step that something we should in fact really point our guns at i so soon as we have decided what to do in the immediate case.

So I just want to raise an issue that has stuck in my mind as I listened to the deliberations the past several days. And one that I believe would be captured if we were able to move to this semi-ideal exponentially-based averaging method that is looking at half lifes of effects, summing them appropriately and with appropriate rolling averages over the calendar year.

A much simpler grosser look at this issue would be, however, to

ask whether -- well -- come back to what I still think is central to the EPA's planned approach now and may still be the way we would proceed if we could get to you at the next level with this sort of, how should we say, exponentially weighted rolling sum.

And that is the issue of -- if I do understand the agency's position correctly, we're going to use a lot of science to turn the multiplicity of OPs out there into a single OP. So we're going to use relative potency factors.

And so almost everything else we do the effects of that are going to be a condition on how we make the choice of generating these equivalents, relative potency factors to generating what you might call equivalent exposure levels.

And I see a potential, anyway, I believe, in fact, maybe some actual danger in trying to lump everything together in this way, however elegant it may be mathematically and however essential it may be to get a proper manageable algorithm depending on just how much difference there is in the, say, biological half lifes of these -- effect of biological half lifes of these agents.

So come back to the issue of determining relative potency factors based -- in comparison to methamodophos (ph) based on steady state effects. So dosing paradigms bring us to steady state.

I think the evidence is pretty good that you do get there at least in animal treatment models, exposure of about 21 days or so. And that sounds right to me.

It may not be actually that much different in humans. There are some of these parameters that differ maybe quite a lot. But I happen to know something about the turnover times of cholinesterases in humans. And they may be different. But I don't think they are scaled by a factor of four.

But anyway, let's grant that we have got a, for the sake of argument, we have a way to dose animals and determine with -- be confident that we are at steady state. And that's a comfortable position to be.

So then we can generate based on the tightest available data which we have learned is inhibition in the female rat brain. We can generate some relative potency factors that we have a lot of confidence in. We can use those to convert things back so we can decide that one milligram of chlorpyrifos, which is not relevant anymore, but is equal to 10 or 0.1 milligrams of methamodophos, fine. So we can start adding these things up.

I think that from the admittedly simple minded viewpoint that I have, that would probably be a fairly good way of summing up effects,

and then cumulating effects, I guess that's our business right now, accumulating the effects from exposures to multiple OPs that were coming in in a dosing pattern, thinking of Dr. Doyle's high tech, graphic, but actually very lucid explanation of our problem here, dosing patterns that are either -- they are continuous enough or repetitive enough that they tend to generate, let's say, lumpy looking exposures rather than spiky ones.

And again, in a very simple-minded way, I imagine that is the way we get exposed to agents in food, in water and air for the most part because we happen to live right down stream from the methamodophos factory.

And I think probably a lot of this background exposure that results in 80 percent of the population having detectable metabolites in their urine comes in this way. I feel pretty comfortable about that.

What I don't feel comfortable about, I don't feel authoritative enough to say I feel uncomfortable, therefore, there is something radically wrong, is whether this approach, single method for calculating RPFs based in this way is going to serve as also or equally well with the sporadic exposures that I expect are coming from residential lawn pesticide, orchard -- acute exposure scenarios where I think the Orkin man visits, the house is bombed or the cracks are

coated.

I imagine that does lead to a spiky irregular dosing pattern.

And so that would be just fine if there isn't very much difference in the relative potency factors estimated not at steady state but after an acute dosage.

So if they are really the same or almost the same, I think that's just fine.

And the document we have here indicates without going into specifics that it isn't too far off that maybe two to threefold.

But at least I want to raise for consideration the idea that when we're folding in these different individual compounds into a cumulative assessment, a cumulative assessment where we are actually cumulating exposures based on these equivalent doses, that we need to take a close look at what the relative potency factors would be or are after an acute exposure.

And I would submit that if they are noticeably different, we should think about actually somehow splitting up the algorithm to take -- to decide that for the compounds that are, the very limited number that are still approved for residential exposure, give consideration to either substituting the relative potency factors based on the acute data for the chronic ones or somehow weighting things so that when we are

specifically dealing with the kinds of applications or the kind of exposure scenarios, residential exposure scenarios, that in those scenarios we use a relative potency factors that are derived from a time frame that is consistent with the likely pattern of -- the likely temporal pattern of the exposures.

That's really my only comment.

DR. ROBERTS: Thank you, Dr. Brimijoin.

Dr. Richards?

DR. RICHARDS: Thank you.

I find myself sitting here thinking that I'm sort of the panelist equivalent of the naive rat that has had relatively little exposure to organophosphorus toxicity arguments and so forth.

So I'm starting from the bottom. Not on that chair. And maybe that means that my brain won't be quite as inhibited and I would be looking at things in a slightly different way than the rest of you. I don't want to take that analogy too far.

But my experience with OPs is mostly through what we see in monitoring water sources. So I'm not really that familiar. And a lot of this toxicokinetic modeling stuff is new to me. I'm just happy I can even say it.

But from that perspective, I would say that I had some real -- I

really have found the exposure side of things very interesting, very innovative, very imaginative and quite reasonable. And I have had a real hard time getting my mind around the toxic side of things, the toxicity side of things.

It's basically -- the problem as far as I can discern is that I'm having a hard time deciding what is the toxic effect you are talking about.

Is it cholinesterase inhibition itself? Is that just a measurement endpoint that is used as a surrogate for some other toxic effect?

If it is a measurement endpoint but not an effects endpoint, then what are the health effects that we're concerned about?

It seems to me this is a much more subtle and obscure issue than would be the case if we were talking about a known and established carcinogen or mutagen or something like that.

Then we know what we're trying to protect ourselves against. It is not the cholinesterase. It's the cancer that it causes in that hypothetical example.

In this uncertain context about what the effect we're trying to protect against is, there is one point it asks the question about how long does it take for recovery. Well, the question is what is recovery.

And at least for me, the lack of clarity of my understanding on

these questions makes it extremely difficult for me to begin to think about what is an appropriate interval for exposure assessment or how you match that up with some kind of a response effect.

I think in a sense a lot of the comments I'm going to make kind of echo what has already been said but perhaps in a more general and less specifically toxicologically oriented fashion.

At one point there is a statement something along the lines of, OPP is concerned that Calendex may not adequately permit estimates of risk associated with shorter duration exposures.

I must say that the presentations this morning really helped me a lot to understand even what this question was all about. Because I think a lot of the basic information that was laid out this morning was sort of missing from the question. And that probably reflects somewhat what I have developed as an answer.

But it struck me that that question about, you know, is it adequate to permit estimates of risk associated with shorter duration exposures, it is in itself a rather vague statement.

Again, what kind of risk is associated with shorter duration exposures. Is that qualitatively different from longer term exposures. Was it just a question of how you average things. How high do concentrations have to be in the short term for them to have some

effect that we're concerned about here.

One of the things that strikes me is, unless people talk about acute and chronic issues, is that they seem to be defined in terms of duration and intensity to exposure rather than in terms of effects.

In a lot of other cases that I'm familiar with, you may very well have a different acute endpoint than you do -- an acute endpoint may be skin lesions and the chronic endpoint may be cancer or something like that.

So it gets confusing for me to even figure out how you separate acute from chronic if you are only doing it by the dosing pattern. And then you have to go through this process of somehow averaging or aggregating it over time. The two concepts sort of lose their separate meaning for me.

So I suppose really the gist of all of that is aiming at what really is it that we're concerned about that's the toxic effect. I guess I at least could use some clarity on that.

One thing I thought was worth mentioning as a possible analog, and it actually really is quite close to some of the stuff that was presented earlier, but simpler, is a model that has been used in some herbicide studies involved with ecological risk assessment of herbicides in which basically the herbicide is acting as an inhibitor of

photosynthesis. It is not directly lethal to the plant. Toxicity occurs in effect by starvation.

So you inhibit the photosynthesis. And if the inhibition goes on long enough, the plant dies.

If the inhibition is removed, the plant says, oh, hey, let's make some more sugars and it takes right off again and continues.

And really, all that has been lost in a sense is some time for development of bio mass or whatever.

Now, whether that is important or not is an ecological question. And I'm not really interested in defending this model, but it seems to me that other than the fact that you don't have to do -- in a sense, it is an on/off switch rather than a five-day cumulation or something like that.

But it's very similar. And what you kind up doing is saying, okay, if we can identify the endpoints -- I'm sorry the thresholds for inhibition, then we can simply take time variant data and say, what is the distribution of episodes of continuous exposure above that threshold and link with that the distribution of episodes of recovery or available recovery time. And that is your basic information that you are interested in looking at.

It has in common certainly the same element of this post

exposure, post recovery, except in this case there seems to be a considerable lag time before you reach full recovery.

But that serves as an interesting model that has been explored in a different arena. It may help to serve this process along.

I like very much the ideas that were presented and I would like to see it develop in that direction.

Thank you.

DR. ROBERTS: Dr. Reed?

DR. REED: Now I understand what people say when you get five toxicologists together you get six opinions. At least the perspectives is very different, but I think the agency wants to hear, different perspectives.

I am coming from a risk assessor's point of view. And I'm looking at this situation that part of that issues or hardship is really not unique to the cumulative risk assessment.

The matching of period of exposure and the toxicological database is really basic in all the risk assessments that we do.

And I think within the cumulated risk assessment framework, one thing that stands out to be different is the relative potency factor. How are we going to come to that and so forth.

Let me go back a little bit to the sort of general issues that we

deal with in risk assessment. Short of pharmacokinetic models, I think there is always going to be something that we're not as comfortable with in terms of you, you know, period of time and so forth.

What we usually do, I think majority of people do, with different durations of exposure and different patterns of exposure is to do nodical sets of risk evaluation.

Acute, sometimes people define it as after seven days. I would say within three days at the most, usually, single day kind of spike situation. Having done the single spike risk assessment doesn't mean that there is no exposure the next day or day before.

So you do the spike. You do the acute. Then you do a sort of a subchronic or short term. And I think the agency have always done that. Then you do a chronic.

Then if it's related to oncogenicity, then you do a life time.

I think that sort of four measure period of time frame will still work in this situation and should work. Otherwise, we have to go back and rethink the whole risk assessment for even for single chemical.

As I said, short of pharmacokinetic model being able to use and clearly identify the target organ dose and the pattern that goes to the target organ, it is just going to be not quite satisfying.

And that's okay because we have this mechanism of recapturing all the uncertainties at the very end of the risk assessment in the descriptive part of the risk characterization.

That is just going to make the work of making risk management decision more intelligent in that sense.

So that the risk management decision is not really based on just the numerical thing, the one you seen. So that's okay.

Assuming in looking at the exposure assessment that we have so far, I'm quite confident that it is not a problem to identify a spike in terms of exposure of dose level.

It is not a problem to do the rolling in order to find the highest rolling point within the time frame that you want to match up with toxicity.

So the exposure component seemed to be all there. And it is easy to extract based on what you want.

What I think is -- it is a give and take kind of situation with the time frame and with the different perspective for something in the future is how far we want to go into to figure out what needs to be done, sort of the minimum kind of thing that needs to be done.

One thing is that I think -- I could imagine that the relative potency factor would be different for the acute type of scenario than

the subchronic or the steady state scenario.

So there is -- at least I would like to see a different set of relative potency factor.

Relating to that, for the acute type of exposure, the spikes, I would like to also to reconsider the selection of endpoints.

It might not be brain cholinesterase. If cholinesterase being the common mechanism is something that we're looking for as an endpoint, it could be some other endpoints. RBC cholinesterase inhibition or plasma. It really depends on how the database look like.

A shortcut to that is that, if one does not have time and sometimes I don't have time, so I make shortcuts, a shortcut of that is that the agency seemed to have already looked at some form of comparison between the acute and the steady state.

And based on the table that we have seen, some of them are fairly similar and some of them very, say, three to fourfold differences. You might be able to get a jump or at least a jump start to make that extrapolation. Not to say that in the future you would not finetune it. And this is about the relative potency factor.

I mentioned that the endpoint could be different. The reason I'm thinking of that is also partly because a lot of acute studies that we derive or we could make use of to make threshold decision comes from

FOB studies.

And FOB studies -- well, a couple issues with it.

One is for each chemical, there is different time to peak effects. And that's when the cholinesterase is measured.

At least for the plasma in RBC. The brain, I think, usually are measured at the 14 days at the end of that, at the terminal sacrifice.

So because of the different time to peak effect and the measuring of cholinesterase inhibition associated with that, you might find it a little bit fuzzy in terms of comparing the toxicity based on that kind of data because it was measured at a different point.

The way I understood, time to peak effect is not because of the peak cholinesterase inhibition. It is because some endpoints that we decide to use as time to peak effect. And that's why it is going to be a little bit fuzzy.

I would suggest that some time in the future do a pilot study just based on some high contributing chemicals and see what is doable and not doable with the database on that issue.

This morning we sort of got the model of a continuing high background versus low background. What was going through my mind when I look at this question is that with the higher background I could imagine that there is a sensitivity issue in that if an organism human in

this case have been compromised in terms of having a low percentage of cholinesterase inhibition already as an ongoing.

I would think that the sensitivity of a spike effect would have to take into considerations too in that for clinical science and all that you might see some tolerance with the repeated exposure. But certainly, I have not seen that with cholinesterase inhibition.

So if we're going to use cholinesterase inhibition as an endpoint, then that sensitivity you have to take into consideration if you have high background.

We're arbitrarily using those terms, high and low. We haven't defined what is high and what is low. How low, how high.

In terms of -- when I said that we usually have these four -- when I said that we usually have the four time frame for characterizing the risk, it would look like that from the exposure component if a longer time, sort of a chronic scenario, 30 days, 90 days, a year is going to be a separate set of analysis, then one could imagine that the exposure would always be lower than, say, 21 days or less.

So you might not need to do all these scenarios. You do the scenarios after the steady state, is what I'm saying.

In terms of toxicity for the same thing. If your toxicity reaches

certain steady state, you don't need to go any further unless the endpoint changes. And that is a possibility.

If you look at the chronic exposure and the endpoint indeed it being not different, that you decided that it is necessary to do a different endpoint, then, of course, you have to go back to the different exposure period again.

I think that's it.

DR. ROBERTS: Thank you, Dr. Reed.

Dr. Hattis?

DR. HATTIS: I just want to apologize to people for jumping the gun on the answer to this question which I, in my confusion, gave the response to the previous question.

And I want to also congratulate Lorenz in giving a much more lucid and (inaudible) explanation of what I was getting at, at least the core of it, than I did.

So basically I want to second what Lorenz said about the modeling of cholinesterase inhibition.

And then in response to Dr. Richards' and Dr. Reed's comments, I want to just expand a little bit on this issue of what I had expected to do for the next question about the long term future of revisiting the issue of what the appropriate endpoints ought to be and how we

connect them with the adult rat, adult female rat brain inhibition of cholinesterase to a particular -- (inaudible).

I think to do that I want to kind of remember some of the original impetus for the passage of the F Q P A.

And that was the concern expressed in 1993 NIS document that there might well be relatively narrow windows of vulnerability of developing children that could be more sensitive or differently sensitive to neurotoxins in particular than would be the case for adults.

And so I think that what we want to think about is say, okay, look at what is happening during childhood, during early childhood in humans is a process where different neurons are deciding to survive or not survive.

And they are making all kinds of different connections in part by sending signals with each other that are mediated by cholinergic mechanisms.

So that when we have inhibition of brain acetyl cholinesterase in a young child where this process is happening, it is not too far out to suggest that that might have different kinds of effects, give rise to different endpoints, in fact, at different levels of sensitivity than might be found in adult, in an adult brain.

DR. ROBERTS: Dr. Hattis, if we're going to go into whether or not we have got the right endpoint, I'm not saying that's not a valid point, I think we're going to probably get into that in just a little bit.

DR. HATTIS: We'll get into that next time. Yes. Okay. But just to suggest that the -- as an extension of what Lorenz was saying, we might in the future want to reevaluate how, what our tolerable level of expected brain cholinesterase inhibition might be depending upon the age group. Because both the rates of regeneration might be different in young versus old.

And also the vulnerability to different degrees of inhibition over what time period might be different for young versus old.

And that's such a thing that we can't probably definitively assess today, but seems to me there should be an effort to make that assessment in the future.

And in the meantime, it is not outrageous to suggest that the margin of exposure that might be considered in risk assessment might be different for inhibition, expected inhibition in relatively young age groups than older age groups.

DR. ROBERTS: Thank you, Dr. Hattis.

Dr. Freeman?

DR. FREEMAN: Briefly, to pick up on what Dale was saying,

given that we're dealing with cholinesterase inhibition and recovery in adult female rats as the endpoint, it may be valuable to know if there are differences in adult or young rats or humans in the degree of inhibition and how long it takes to recover from an inhibition from similar types of doses.

I don't know whether you have much on that yet.

From the other point of view of my table here, understanding the relationship of the temporal characteristics of the hazard endpoint and the temporal characteristics of the exposures from water, diet and residential pathways, requires that the temporal characteristics of the exposure pathways be similar.

In the document we received it says, regional differences in pesticide use are major considerations in appropriately estimating exposures from pesticides in drinking water and residential uses.

I would argue that this is also true for diet and -- my saying that is not simply a matter of wanting consistency in the way the assessments are done across the three pathways, but that it is important to the quality of the assessment to take into account regional and temporal differences in diet and pesticide residues.

To give an example, during the presentation on the water model, a figure of California pesticide use across the year was presented.

I think that was a powerful example of why it is important to evaluate food pesticide residues in diet by region and season of the year.

There are growing areas in the country. California and Arizona are prime examples that restrict importation of commodities that they grow themselves.

That being the case, the diets of the individuals living in these regions will be influenced by the local foods in their residues more than ones from other areas during the time periods that the local crops dominate the market.

Connected to that is a concern that pesticide treatment of home gardens is only treated as an influence of residential exposure but not on diet.

It is likely that these occur jointly during the same time period as the garden vegetables are treated with pesticides and then consumed.

This will add some complexities to your model. These things are not independent.

But consumption of locally grown fruits and vegetables is common. And in many regions of the country, they are important seasonal additions to diet, and hence to the exposure to the people in

those areas.

DR. ROBERTS: Thank you.

Dr. Heeringa?

DR. HEERINGA: Just a few brief comments. I have to confess that scientifically I'm probably about as far removed from this subject as anybody here on the panel.

But in some ways, that places me in a position sort of evaluating what I have heard on this particular topic.

One thing that are clear to me in the facts here, the points of departure and the relative potency factors and I think even the effects level that we have seen in these presentations are all based on steady state studies that really in my naive view closely resemble patterns that are more like the chronic exposure pattern and the acute exposure pattern.

I have seen nothing on the scientific discussion in the past two days that suggest that acute events have a different endpoint with regard to cholinesterase except to set the chronic clock running at a fairly high level.

In other words, there is obviously a much more complex mechanism that we don't understand here. But I have seen no discussion of outbreaks or sores or people fainting or people unable to

function or loss of motor coordination or activity from these acute doses.

Now, some of that must be there and possibly in the studies. But even at the high dose levels, as I understand it when we are looking for steady states that we go for steady state activity at even higher dose levels in the female rat test.

So again, unless there is other evidence that we haven't heard here, I see an absence of evidence. And that doesn't mean effects don't exist for what these acute effects would be on cholinesterase inhibition.

I very much agree with Dr. Rhomberg's model to roughly model bio available levels of OPs on a given day as the sum of the current day's dose and half life depleted doses from the prior days.

That's an excellent suggestion. Because I think it really reflects cumulative processes that are very realistic in normal exposure patterns.

Also, one additional comment that I would have, in the process of averaging, thinking specifically for the chronic exposure path, is the averaging of daily exposures over a window that centers on the current day is actually a form of smoothing.

I think it is much more realistic to create what we would call a

moving average as opposed to a window average. That is you average over the previous 21 days or the previous 14 days. Because it reflects, again, the realistic pattern of accumulating exposures in the human body.

The other thing that it would allow you to do, and I think this is a piece that I don't understand and I think the toxicologists are going to have to help us inform, is it would allow you to look at the leverage of acute event that comes on top of a period of fairly high exposure.

In other words, if you computed your chronic exposures as an average over previous time, any blip in that chronic exposure curve would probably be the result of an acute event on a particular day.

And again, acute events in the future, while they may be important in the future, they are not really important at this point to exposure levels.

So I think you would have full information of the impact of acute events if you created your moving averages as a function of averages over preceding days, unless there is something that my colleagues see that I'm missing here. I think that even for chronic analysis I would use Dr. Rhomberg's model to get daily sort of available exposure levels and to use moving averages over a

retrospective period of time.

I don't think anything is lost there I think and I think something may be gained in terms of information.

DR. ROBERTS: Thank you, Dr. Heeringa.

Dr. Durkin?

DR. DURKIN: Under advice of counsel, I'm going to restrict my remarks to the exposure spike issue with the understanding that we'll get other things soon.

The ideas raised by Dr. Rhomberg and endorsed by some of the people around the table are interesting ones to me that the agency could explore. They are contrary to what I will be recommending.

But the only thing that I would want to caution here, and I very much doubt that there would be any disagreement around the table, if you adopt something like that, at least make an attempt to determine if it's consistent with data that you have.

And the reason that I am uncomfortable, not with this suggestion, but I guess I don't have a high optimism that you will validate it well is that the temporal relationships in acetyl cholinesterase that I'm familiar with are God awfully complicated. And they don't seem to follow -- the rats just don't behave. They just don't do first order things all the time.

And there is some human data out there that have me just totally puzzled. And again, they just don't fit a simple pattern.

Nonetheless, if you do find data to support the approach, I certainly would be the first to endorse it.

My somewhat simplistic recommendation, and I will quote, thus the agency, at this time, goals should be humble, and one of the things that I think that you could look at, I think you have done a Dandy job with steady state, I originally recommended the first time I was down here that we incorporate time as an explanatory variable.

I think that's insane as I have looked at the issue further and come to better appreciate the data that you have.

I am much closer to my fellow risk assessor right across the aisle here taking perhaps a simpler approach if nothing else seems to pan out. Because I think you really have to do to address the spike issue.

But at very least come up with some acute numbers. And I think we have talked about this in the past.

You typically have acute numbers for a lot of the pesticides anyway. You are currently coming up with one day RFDs, or whatever you want to call them, in drinking water has been doing this pretty much forever. So that's not hard.

I think it is relatively easy. I'm not the least bit surprised for the OPs to see the close correspondence between the longer term and short term. I fully expect that. I fully believe it.

So if Dr. Rhomberg's very elegant idea doesn't appear to be sufficiently implementable quickly or doesn't seem to fit the animal -- and by all means we really have to be ruled here by the animal, they make the decision, and by the available studies, especially that we have on people, and some of those are very good, if that doesn't pan out, I think you really can take a simpler approach.

Now, how you actually implement it, when is a spike going to be considered acute, when is it going to be considered not, you know, that is, I'm afraid judgmental.

And I don't think that we can make up a cookbook recipe here.

But I certainly think you people have the capabilities to make those decisions, make them clearly, articulate them, go out on the limb, and then invite us back so we can saw it off.

DR. ROBERTS: Thank you, Dr. Durkin.

Comments from other members of the panel?

Dr. Bull and then Dr. Conolly.

DR. BULL: I'm going to make some of the same points, but in a slightly different emphasis, I think.

The issue you got in front of you is a common mechanism. That common mechanism you chose to be cholinesterase inhibition.

Cholinesterase inhibition may not actually account for all the toxicity the member of that class. But that's fine.

You have kind of put part of the issue, not all the issue that Dr. Richards brought, you kind of have to put that to the side.

So you are really only addressing in this process toxicities that arise from cholinesterase inhibition. It is important not to forget that.

Given that focus, then there is no better integrator of toxicity, I mean, your measure here than the cholinesterase inhibition.

And the issue about acute and chronic I think is a trivial issue almost in a way, because acute doses will have certain magnitudes and will give certain rise to certain cholinesterase inhibitions.

And I think you have essentially made some kind of decision. Maybe not as to what the point of departure is absolutely yet, but when you say benchmark dose 10, that's probably not going to be bad for either acute or chronic.

You are talking about things that are in the weeds. As long as you are talking about effects that arise cholinesterase inhibition.

To me, that's best addressed in a pharmacokinetic model similar to what I think a formal model wouldn't be that much more difficult

and probably be -- than what Lorenz said. But that's fine.

The main variable there, though, is the recovery time. And the recovery time has two, at least two components.

I'm not going to call it a pharmacokinetic model because in my mind that starting to get somewhere else. And you are not talking about kinetics of the parent compound. You're talking about the kinetics of enzyme recovery.

That has at least two components. That's a spontaneous regeneration rate and enzyme resynthesis rate in whatever compartment you are talking about. It doesn't make any difference.

Then that brings it back to the question that Dr. Brimijoin -- the whole weakness of this thing is not trying to use a pharmacokinetic model. The whole weakness is how much confidence you have in those RPFs. Because those RPFs will vary primarily based on differences in the hydrolysis rate of those phosphate esters.

The enzyme synthesis rate will presumably be more or less independent of which agent (ph) caused the inhibition.

So that -- as long as you know that that is what is accounting for differences in RPF, you perhaps can even repair those. And I think there is probably data out there that tells you how stable those are.

This is not my area. But it seems to me that that's a very doable

and, I don't think, difficult thing to do.

The only thing that I think that I would say, and this gets more to sensitive populations and whether humans are the same as the rats, is you really would need -- you would like to have the big variable here as far as the subject is concerned is in fact those resynthesis rates and how they may vary in different departments and in animals of different -- in humans mostly, humans of different age.

That's the variable that's important here that one, I think, needs to deal with when you start trying to slide from cholinesterase inhibition at some level over into some toxic manifestation you feel arises from that.

That's all I have.

DR. ROBERTS: Thanks, Dr. Bull.

Dr. Conolly?

DR. CONOLLY: Let me just pick up on the point Dick was just talking about.

Dick, I think the RPFs actually would be strongly influenced by pharmacokinetics as well as things like hydrolysis rates. Because a lot of these OPs do require bioactivation.

And bioactivation rates are going to be determined as a potency.

Let me move on to some more prepared comments that I made,

though, in response to this question.

And this first comment is an effort to hopefully put some of the other comments that have been made by the panel members in a bit of context.

I have some background, some experience in actually developing very ambitious complicated models and then using them in risk assessments.

And what we find, and we're seeing examples of it here today, what we find when we start to develop mechanism based models and participate in the thinking process that accompanies this development is that we're always thinking about the next step you know, about how the model could be refined.

And this actually is in distinction to the more static situation you have with policy based approaches to risk assessment where you just plug a number into a formula and you get an answer out.

But when you do take the more ambitious approach, the mechanistic approach and want to actually complete a risk assessment at some point, it is really necessary to draw a line with respect to the technical development of the various models that are feeding into the assessment, in this case, the cumulative assessment, freeze the model development process at that point, and then go on to complete the

assessment.

So, of course, refinement of the models and better understanding of the underlined biology can always contribute to future assessments.

It can be discouraging if you are always being told about the things you might do or you could do and you really have a job to get on with an assessment.

So I just want to make the point that sometimes you have to stop and say, okay, we're going to just finish up here. And maybe the next generation of models can contribute to the next assessment. That's one point I wanted to make.

I was told -- actually I read it in the one of the files on the CD that there actually is a PBPK model for three 0Ps. I gather that I think maybe Jerry Blancato (ph) has developed.

So we're not quite as far away from having maybe the most desirable tool for pursuing these kinds of assessments as we might have thought we were.

But it did occur to me when the presentation was being given with the acetates and the questions were being asked about these various alternative exposure scenarios, you know, how to evaluate those, how to think about them, is that you can actually take Jerry's

model, presumably existing model, and feed those kinds of exposure scenarios into it and see how cholinesterase inhibition varies as a function of exposure scenario.

You actually have a tool for doing that right now. It clearly wouldn't be the same as having a PBPK model for all 29 OPs. It is not what you would like to have. But I think you would find it would provide incites and it might well bound the problem that you are trying to address in some ways.

So I would encourage you to think about exploiting as fully as possible the tools that you do have at hand in trying to answer that question.

Finally, I think I mentioned earlier in the week that I got tasked in January with reading the cancer guidelines. There was a public comment period that finished up late in January.

And so I actually read every page of the cancer guidelines, believe it or not.

And it has been striking sitting through these meetings here over these last few days how many of the issues that arise in the cumulative assessment for OPs are also considered in detail in the draft guidelines for carcinogen risk assessment.

For example, identification of when children are or are not at

greater risk than adults. Some thoughts on how you evaluate an MOE to decide whether it is big enough or not, whether it suggests that you are okay or whether you might have a health problem.

Thoughts in the guidelines about the benefit of inclusion of some mechanistic data without the development of what they call a full case specific model which in the present context would mean having a full blown PBPK model for all of your compounds.

The other thing Lorenz was talking about, maybe you can include some biological data. You don't have everything you would like. But the cancer guidelines are very clearly supportive of that approach.

If you have some biological thinking that you can bring to bear on the problem, then do it to the extent that you can.

So I would encourage OPP to work with the authors of the cancer guidelines to ensure -- first of all, it would give a more harmonized approach, which for somebody who observes the agency from outside it is always nice to -- it is easier to work with the agency if what is coming out of the agency is harmonized across different groups.

And also, just frankly, to ensure that OPP obtains the full benefit of the thinking that has gone into the development of the

cancer guidelines. Because so many of the issues in there are relevant, I think, to what you are grappling with here in the cumulative risk assessment for OPs.

I'll leave it at that for now.

DR. ROBERTS: Thank you.

I was going to jump in with my own comments, and then we'll get to Dr. MacDonald. Let me sort of give you my two cents on this.

First of all, I did like the suggestion that Lorenz made. It makes a lot of sense to the extent that I have been able to think about for a half an hour or so now since I first heard about it. I think it is worth exploring.

It may be once you get into it you will hit a wall in terms of the data that you need to do it or that sort of thing. But you won't probably find that out until you try and do it. I think it is worth exploring.

I also like Rory's suggestion about exploring some of the existing models.

Whether or not you can either of those within the time frame of producing your first document, I don't know. You will know better than I do. But I think that those are things that should be looked at in the near future if not by whatever deadline you have to satisfy this

summer.

In the event that you can't implement those and sort of in the meantime, on the issue of whether to use a one day rolling average, it seems to me by the virtue of the way you have defined your benchmark response as a 10 percent cholinesterase inhibition, there is no time factor in there.

It is not 10 percent on average over certain period of time. It seems to be implicitly sort of an instantaneous endpoint. So soon as you hit that for any given period of time, you are there, which implies that probably the one day or the peak exposures is the most appropriate for the purposes of comparing with the benchmark response that you picked.

And so the only rationale for using a rolling average is that it sort of matches better the way the studies were done to get your benchmark response.

And I think really what you have to say is that the benchmark response developed based on 21 or 28 day exposure is a reasonable he estimate of an acute benchmark response, which is what we really want to work with.

And we don't have the data to do that or do that as well, at least as I understand your presentation of the information. But we have got

some steady state data. We can get that. To the extent we can compare that with the information we have, it indicates that it is a reasonable estimate of what an acute benchmark dose would be.

Now, the problem, of course, is that you don't have good data to get an acute benchmark response. You don't have a lot of data anyway. And most of the data you have are not the right kind of acute data, because, as you have pointed out, what you are really looking at is an acute pulsar and acute dose on a background of some level of chronic exposure that is going on.

So you really need acute dose response data that are generated under those circumstances ideally. And of course, depending on whether it's a low background or a higher background, you could different responses from the same dose depending on what level of compensatory activity is going on in the body.

I mean, at low doses you might get some sort of hermetic response where it is lower than what happens at a higher dose, higher background. So that's going to be complicated.

Obviously, you are not going to have those data soon, although I think that's ultimately the kind of toxicity data you need to get the benchmark dose that you really want to plug into this analysis.

So in the meantime, I think you are sort of stuck with what you

have got and making the best argument that you can that it is a reasonable, acute benchmark response.

Again, that would leave me to concentrate mostly on the one day rather than trying to do a rolling average.

On the matter of incorporating time into the response, I think -- there have been a couple comments about the importance of doing that.

I think it is appealing for the toxicologist to think about that it is not just an instantaneous achieving of a certain inhibition of cholinesterase, but it is probably a function of cholinesterase inhibition and time in some way that we don't understand or at least I don't understand. There is people around the table that know much more about cholinesterase toxicology than I do.

But my impression is that we really don't have a good understanding of how exactly that all works to come up with the best way to incorporate both inhibition and time.

And so until you do that, I think you sort of need to acknowledge that that's probably the best dose metric, but we don't have that -- a response metric. But we really don't have that. We're having to sort of deal with just a given level of inhibition instantaneously. And that's what we're going to go with, but realizing

the imperfections of that.

There were also some comments about the relevancy potency factors. I expressed my reservations about the approach two days ago. And those reservations still stand.

I think that given the way that you have had to estimate the relevant potencies, there is going to be error. There has to be. Because of sort of the fundamental underlying assumption, everyone acknowledges, has been violated.

As a practical measure, I think you are probably going to need to go the way that you have. But I think it is going to be important to acknowledge that there is an error due to that.

I guess the most unsettling thing for me is that I don't think we have a good sense for the magnitude and the direction of the error that we're introducing into this by being forced to do these relative potencies the way we have done them.

So again, I think to the extent that some sense can be derived about the magnitude and the direction of error, that would be useful to incorporate into the analysis. But again, until we get better data or better ways to do this, I don't have a great suggestion for how to fix that problem.

Those are my comments.

Dr. Durkin and then Dr. MacDonald.

DR. DURKIN: Stephen, I just want really clarification on what I think I may have heard you say.

And if I'm correct, I totally disagree. But I thought I heard you say that in terms of how the EPA should characterize risk, they should take their, let's call it, the steady state ED 10 and compare that to the one day exposures rather than averaging.

And if I misunderstood you, I apologize. If I didn't misunderstand you, I think that is not a good approach, because I think the agency has demonstrated to us both for this session as well as previous ones that the shorter term responses are really quite different.

And they focus on the steady state in order to get some stability in relative potency. That has been my understanding. I may be totally wrong, again.

So I do think that the issue of how to handle spikes in my mind, anyway, is indeed a difficult one as the agency has presented to us. In terms of the steady state ED 10 that you have come up with in whatever final ED you select, it is steady state.

And it would seem to me to make a certain amount of sense to do a time weighted average of some sort rather than to say we are

going to use this steady state ED 10 to characterize risk from these spikes, these way high spikes that come out of nowhere and don't last for long.

Because I think it is for those things that you might want to consider some sort of shorter term dose response assessment where indeed the relative potencies might be quite different as you have pointed out, I believe.

DR. ROBERTS: I think Dr. Doyle is going to clarify this for us.

DR. DOYLE: No. I'm going to ask a question.

DR. ROBERTS: Okay.

DR. DURKIN: Steve, we are in trouble now.

DR. DOYLE: I think that something is happening today is something that was discussed earlier in the week.

And there is a distinction between BMD 10 used for RPFs and BMD 10 for point of departure. And some of the discussion, I think, is mixing the two. Could you perhaps tease them apart as you have expressed your opinions on the two? Because I think there are different considerations there.

In fact, we only have one BMD 10 that we're using as a point of departure for one chemical whereas we have the whole range of BMD 10s that we are using for the RPF issue.

So could you clarify in your discussion which is which?

DR. DURKIN: I was specifically looking at point of departure. And as I have said before, that it is at that point of departure that you have to have your relative potency expressed.

So they are kind of synonymous. But I was specifically concerned with points of departure.

DR. ROBERTS: I was too. And I think that that then sort of clarifies the issue.

And then is the benchmark response a certain level of cholinesterase inhibition over a certain period of time or as a result of an exposure over a certain period of time or is it an instantaneous response?

DR. DOYLE: The benchmark doses that were used for the steady state determination are the result of 21 days or more of dosing of rats in all cases.

DR. ROBERTS: That's true.

Again -- it becomes very important at least in my mind how you define the benchmark response.

DR. DOYLE: I agree. That's why I'm asking as you discuss it to that bear that in mind. And then also the application of that value either to estimating a risk or comparing between chemicals.

DR. ROBERTS: If you want to know what the margin of exposure is relative to a one day exposure that will produce 10 percent inhibition of cholinesterase, I suppose that's one thing as compared to a response over some time or a dose over some time that would produce on average a 10 percent.

So I guess I need some clarification -- it depends on how you approach it. I guess I would need some clarification from the agency in terms of what is the -- are you defining the benchmark response based on the animal study, or are you defining it -- are you using the animal study to try and give you information about a benchmark response that you have in mind?

Is that clear?

DR. DOYLE: Yeah. I think so.

We used the animal studies to provide information to give the shape, the response of the model. So I think it is more the latter. We're trying to use the data from the animal study to develop the benchmark dose.

However, there is a confounder in this question because all of the data that we used were 21 days or greater.

The question is whether that impacts the discussion.

DR. ROBERTS: Dick Bull and then Lorenz.

DR. BULL: The question is how much more inhibition are you going to allow for single dose.

DR. DOYLE: None.

DR. BULL: That's your point, I think. And if you are not going to allow more than 10 percent as in that situation, well, you have already defined yourself into that corner, and I don't think inappropriately, but that would of course take a larger dose on any given data approach than it would take as a daily dose to approach that over a 21 or 28 day period.

Your external doses will be quite different.

DR. ROBERTS: Dr. Rhomberg?

DR. RHOMBERG: I just wanted to agree with Dick on that.

If you think about it, the steady state experiments didn't have any toxicity in them at all. There weren't any determinations of toxicity. It was just determinations of cholinesterase inhibition.

As I said earlier on in the meeting, I think that the rationale that the agency deployed for why they wanted to look at relative potencies at steady state was sound.

The question of whether the relative potencies will be different for acute things is worth maybe -- because this has come up with several commenters, is worth a second of thought.

Obviously, if you define relative potency -- you have to think about how you define relative potency. Because in a short term experiment, you won't have any steady states to compare.

You can't say, well, we compare steady states in a short experiment. What would compare.

Presumably, you compare peak levels and say the things -- the relative peaks that are provided or the relative doses it takes to make a certain peak at a certain level is what would define the relative potency.

Now, again, I'm simplifying pharmacokinetics. As long as the pharmacokinetics are linear, which granted they may not be, you will get the same relative potencies out of the steady state issue that you will get for the peak issue.

For linear models, those should be the same. The ratios of those things among chemicals should be the same. And the long term ones should apply to the short term ones.

Now, there is a ways to screw that up with all sorts of funny pharmacokinetics and so on like that. Of course, there is no way around that but to do all of the experiments.

So I think that's worth noting.

DR. ROBERTS: And I agree.

Dr. MacDonald.

DR. MACDONALD: I trust dealt we have dealt with this topic. I want to get back to the rolling averages. Because I saw the -- the rolling averages on the windows on the model inputs, diets and residues, in particular, in attempt to generate auto correlation in the inputs at the expense of extreme values.

And I think that's a good, simple way of doing it. I don't think doing that -- the fact that you are averaging ahead and backwards in time really matters.

And it is quite a separate issue from taking, computing an accumulated exposure as a weighted average of past exposures. I think you could actually do both on the same model.

DR. ROBERTS: Dr. Conolly?

DR. CONOLLY: This is just a clarification from the chair.

A couple of people have made comments about RPFs in the context of answering this question. I prepared some comments about RPFs thinking I would offer them in response to the second question.

And I just want to know if I should hold off or go ahead with it now.

DR. ROBERTS: Why don't you hold off and then we'll revisit and hopefully come to closure on the RPF issue in the next session.

Are there any other comments about our sort of relationship between rolling averages and toxicity values?

We have had a good discussion. I don't know to what extent we have given the agency any clarity of direction.

DR. DOYLE: I think quite a bit, actually. And also as was pointed out, long term as well as for this assessment. So thank you all.

DR. ROBERTS: If there are no other comments on this one, let me propose that we take a 15-minute break, and then we'll tackle the last question.

(Thereupon, a brief recess was taken.)

DR. ROBERTS: Dr. Doyle, are you ready to pose the second question to the panel?

DR. DOYLE: I believe, yes.

DR. ROBERTS: I think they are trying to get the question up on the screen. But if you could go ahead and read it for us, that would be fine.

DR. DOYLE: Question 2.

In the Preliminary OP Cumulative Risk Assessment, Section 1 H lists a number of potential follow-up activities proposed by OPP.

This list is far from exhaustive. Does the panel recommend any

additional follow-up activities or sensitivity analyses beyond those listed.

And does the panel have any thoughts or recommendations about how these additional analyses should be conducted.

Which activities should be receive the greatest priority.

DR. ROBERTS: Thank you. I think that we're going to try and get the list of those activities put on the screen to sort of refresh everyone's memory about what the agency already plans to do.

This question then asks our opinions on any other things and what should be the highest priority.

Before we get into the response to this, let me just tell the panel, let's go ahead and focus our responses on kinds of things that they need to do in terms of follow up.

I realize there is a little bit of a gray area. But as soon as we wrap that up, there are folks that want to bring up some other issues of importance that are not necessarily part of specific follow-up activities.

So let's go ahead and tackle this particular question.

I believe we're going to go a little bit out of order. Dr. Conolly would like to get his comments in first because he has to leave early.

DR. CONOLLY: First of all, I would just like to say that the

situation here where the agency is actually asking us about how to do it better, differently and better in the future is to be applauded in its own right.

It is really great, I think, to see the agency not only doing a job as well as can be done in the present moment for cumulative assessment for OPs, but also thinking about how to do it differently and better in the future.

My hat off to you on that score.

I just wanted to make one comment about relative potency factors. And this is very much in the spirit of how you might do it differently in the future as opposed to I don't necessarily want you to redo any of the current effort based on this particular comment.

But I do want to get on the record this statement. From a mechanistic, biological perspective in thinking about pharmacokinetics and pharmacodynamics, it's clear that the use of relative potency factors is undesirable.

I made the analogy a day or two ago that RPFs are analogous to thinking of individual OPs as sort of different kinds of fruit like apples, bananas and pears, and then calculating what an average fruit looks like.

Just as there is no such thing as an average fruit, so the use of

RPFs is at best an approximation to the actual pharmacokinetics and pharmacodynamics of the components of the mixture.

We know we are building an error there. It is unavoidable, of course, when the data aren't available. But there is a science-based solution to this problem, which those of you that know me will know what I'm going to say next, which is to use PBPK models for the individual OPs and then to include the appropriate interaction terms so that the individual models can be combined.

And then when this ideal approach is used, it obviates the need to calculate RFPs as your approach that's being used captures the pharmacokinetics and cholinesterase inhibition kinetics for the individual components of the mixture.

And these are used directly then in the assessment without modification. So there is technical approach to this work that doesn't require calculation of relative potency factors.

I think some of you actually in your thinking about where these kinds of assessments will be going in the future are already thinking along these lines.

I know that one of your future aims in that section of the document talks about developing PBPK and pharmacodynamic models.

So I'm sure you are already thinking along these lines. Really,

the purpose of my comment is simply to encourage that and to get in the record that there are ways of getting away from relative potency factors.

Thanks.

DR. ROBERTS: Thank you, Dr. Conolly. I think that is an excellent suggestion.

Let me, then, go back to Dr. Hattis for his comments.

DR. HATTIS: I would like to suggest a number of follow-up activities.

And I should stress that these are not necessarily limited to the next three months, but that these are more looking toward the slightly more distant future than that.

And I think that I want to second something that Chris Portier evidently raised a day or two ago.

And that is there is one particular promising avenue that might even be used a little bit in the near term, is some further exploration to compare the modeled distribution of exposures to sets of pesticides that yield a common urinary metabolite.

I understand that urinary metabolites aren't necessarily unique to one. But at least you should be able to know which chemicals are reflected in a particular metabolite to yield some comparisons of what

you would expect by applying a basic pharmacokinetic urinary excretion model to the exposures to those things that yield that same metabolite and say, okay, what does the distribution that you would predict looks like for the current exposures of the U.S. population and what is the distribution that is evident from the NHANES 3 study.

Because that seems to me that that -- it is too strong to call such a juxtaposition an attempted validation.

It seems to me that that would give you a clue as to how you might want to tweak the model to make it more faithful to the bottom line biological exposures that seem to be indicated.

Some of the basic tweaking that you could think of is in fact by assuming some different degrees of auto correlation of the dietary exposure that occur on different days.

Although, by and large, by urinary measurements, these are likely to reflect a very limited number of days, if not just one day of exposure. So it may be that it doesn't tell you anything about auto correlation, but it may well tell you a lot about how reasonable your model of daily exposures distributions is -- are.

I think it is also important to pursue this issue of multi-day modeling in the actual buildup of cholinesterase inhibition over time in the face of reversal regeneration rates in people.

You are not going to have that for the reign. But you will -- you should be able to get some information about red cell and plasma cholinesterase reversal from observations on people who have been poisoned.

And then, you know -- there is going to be a body of data. There is going to be a body of maybe observations from more -- less seriously exposed people that were exposed during occupational populations and then followed with regeneration -- with recovery rates followed over time.

Comparing those with some expectations from -- the direct projection from animals may give you important clues.

And I think an important longer term effort is to some extent respond to the point that was made several months ago in a panel meeting by Dr. Needleman, and he put it in terms of validating the relative potency measures for various effect endpoints, behavioral respiratory enervation, behavioral developmental changes versus brain, versus red cell cholinesterase, versus plasma cholinesterase in the experimental animal systems.

I tend to avoid the words like validation because I think it's more a one way comparison. But I think that nevertheless, some juxtaposition of whether the relative potencies you get out of the rat,

brain system are the best measures of relative potency for predicting all the different effects of anti cholinesterase agents is, I think, a worthy investigation.

And also would give you some beginning clue as to reevaluating this whether you want to choose in fact the ED 10 for rat brain cholinesterase as your point of departure or whether you want to choose some other level depending upon, say, the relative sensitivity of younger animals versus older animals for subtle neuro developmental effects.

It is not obvious that the ED 10 is the idea -- it is a good first guess, but it is not necessarily the golden truth that is going to last for a decade.

I think that some derivation of distributions of human -- that's right. I already said that.

The next item that I think should -- there should be some attempt in the near term but maybe more fully attempts later on is right now the analysis is purely a variability analysis.

There is no uncertain analysis. There is some modest amount of sensitivity analysis perhaps that you can do with the current system by relaxing specific assumptions, eliminating particular pathways, eliminating particular chemicals that get useful information.

But at some point it seems to me people are going to ask you, maybe people in Congress might ask you even, for some more formal uncertainty analysis.

So how well do you know this answer. And you are going to need to develop uncertainty distributions that reflect --

This is now, again, going to this issue of two dimensional. But essentially, you have a certain guess about different factors that cause people to vary in their exposures and their responses. You have information from Dr. Setzer's wonderful work about the uncertainties even of the relative potency factors.

So it seems to me you should try to propagate some of those uncertainties that can relatively readily be defined to, say, okay, if we are -- have a -- instead of median estimate of the relative potency factor for this one, if for some reason we were at the 90th percentile of our estimate of that, holding everything else constant, how much would it change the results, or you could do the whole system propagating uncertainty -- some reasonable estimate of the uncertainties of several different kinds of parameters describing both base levels of exposures and different toxicity relative potency issues.

I think the suggestion made by one of the regulated company representatives was reasonable if it is true that there are cases where

the model uses more than 24 hours a day, that then some limitation should be imposed on the modeling so that that doesn't happen.

It seems to me that should be a relatively modest adaptation that would avoid the need to explain why it is reasonable to assume more than 24 hours a day if it is true.

I think that to the extent that there are volatility of particular organophosphate agents, it would be reasonable to add some inhalation exposure to the lawn type scenarios.

Or to the extent that there is, you know, dust being kicked up, then you could inhale some of the entrained dust.

I think it is certainly reasonable to explore this issue of school day exposure, school or day care exposure even more appropriately for an exposure for very young children.

It's by no means unreasonable to expect that diazinon or something else was used at one time for control of cockroaches in day care centers. Maybe it's -- maybe those uses have been phased out. I don't know that. But that's possible.

Finally, there is a need to collect in the long run some longitudinal data sets for dietary exposure particularly, perhaps for some other kinds of recurring exposures.

You don't need the same thousands of people that are routinely

done in the Department of Agriculture studies. But it seems to me that some modest amount of data that, say, spend a few weeks per person for three or four periods during the year would be invaluable in allowing you to assess the degree of auto correlation of the dietary exposures and calculate long term accumulated measures of internal exposure and cholinesterase inhibition.

And that would just avoid a whole lot of hand ringing. And also more appropriately, allow you to estimate risk.

I think the current model is very good for pointing you in the direction of what is the most likely source of controllable exposures of, you know, giving rise to high days, but in a long run for evaluating dietary exposures.

In particular, you are going to need to know about this auto correlation that you can only get really by some modest amount of additional observations to answer this point.

DR. ROBERTS: Thank you, Dr. Hattis.

Dr. Rhomberg?

DR. RHOMBERG: I think those are some good suggestions that I would endorse them. Obviously, I made just a bunch of suggestions already. So I won't add, I won't reiterate them, only to point out that I think the issue of cross pieces extrapolation has to be more explicitly

and carefully looked at.

There is a lot to be done in tying levels of cholinesterase inhibition to toxicity, both in the short term and the longer term. And I think I expounded on that before. I won't go on too much about it anymore.

I frankly would have liked to have seen an attempt to try to combine roots by the degree of cholinesterase inhibition rather than this margin of exposure harmonic mean averaging.

The harmonic mean method implicitly has linearity in it.

Now, it is probably not too bad because it probably is more or less linear for cholinesterase inhibition.

So it probably works okay, and I don't really expect you to get a different answer. But I guess I would prefer that if you are really doing it on cholinesterase inhibition, to do it on that. That's a common currency. I know there are some technical difficulties to doing that.

And I would also like to see taken seriously the home gardening -- food from home gardening exposures, which seems to me to be something several people have mentioned. And I agree as a potentially important thing that should probably be brought in.

DR. ROBERTS: Thank you.

Dr. McConnell?

DR. MCCONNELL: I too will not add to what has been said before. But it is sort of a taking what Dr. Hattis said maybe a step further.

I had a brother-in-law that was a time study engineer. I guess now they call them efficiency engineers.

And I talked to him -- used to talk to him a lot about how he did his job and stuff. He said that the first thing he does is when he went into a factory or whatever was take a look at it and see where the bottlenecks were.

In terms of bottlenecks, for me, it looks like one of your bottlenecks as was explained to us yesterday that you can't get as many water samples as you would like because of the chemistry involved.

So as I explained yesterday, I think it might be worthwhile to have your chemist sit down -- and I would certainly encourage industry more so because I think your chemists are paid more and you probably have a lot more of them to do the same thing that I'm going to propose now.

And that is to sit down and find a quick efficient, by that I mean not technically difficult, and inexpensive way to find total

organophosphates in water and other media.

I'm not a chemist, but I'll bet you you would be surprised that if you posed the question to your people you might be surprised what they could come up with.

And certainly, the worst answer that you would get is we don't know of anything better, more efficient, less expensive. I mean, that's an answer. But if you never pose the question, you will never find out. So I would like you to do that.

And certainly, if you could come up with a technically easy method of analysis, it doesn't -- you need to be in the ballpark for what I'm talking about. You don't need to be to the parts per trillion.

If I can get down parts per billion, even parts per million, I know whether I have a problem or don't have a problem with that particular sample.

Second is I'm wondering if in terms of acetylcholine evaluations, if there couldn't be an invitro system developed.

After thinking about that, I have a few ideas. I won't get into them now. But I bet there is a biological method that you could use to determine -- the potency, is what I'm talking about, in a very efficient way.

Again, I'm not an expert in this area. But if you don't ask the

experts the question, again, you will never find out.

And finally, as I propose at every one of these meetings, occasionally you need to do a reality check.

And by that I mean that after you estimate all these levels that you think a person is exposed to, certainly, there has got to be ways of evaluating people that are exposed via their urine or some other invasive way to find out what the levels of the metabolites or products are in their urine to see how close your estimates of exposure were.

I mean, are these off by an order of magnitude or by a factor of one or two. At least you will know that we're overestimating, underestimating the true dose by doing those kind of things.

And with that, I'll stop.

DR. ROBERTS: Thank you, Dr. McConnell.

Dr. Durkin?

DR. DURKIN: I only have two things. And really one of them Dale has beaten me to the punch on. I just want to endorse it rapidly.

Again, this is not necessarily a criticism or something that need be done in three months, but just something to start thinking about.

I totally agree with Dale that you have done some fascinating dose response work here. And I think it could be useful to attempt to incorporate the uncertainty -- on the uncertainty, the variability, the

whatever, squishiness of your dose response assessment into your risk characterization.

I don't think that is a trivial matter to do. I'm not sure it is super simple. I think when you actually got down to look at the code for all of that, it might even get a little hairy. But it is something to think about.

The other thing that is again very short and is just a soap box of mine, the work that you have done on addressing the potential toxicologic interactions of the organophosphates has gotten progressively better with every draft.

I don't pretend to assert that I think it's a show stopper here. But the agency has recently come out with guidelines for mixtures risk assessment. I know that you are aware of those. They probably get thrown in your face daily.

You may want to expand your discussion somewhat. I totally endorse and agree with your basic assessment that in the low dose region things will indeed be additive or at least noninteractive.

The nasty point gets to be defining low dose.

So it is just something for you to think about over the longer term, because people will raise to your attention repeatedly the well-known interactions and the complexities of the

organophosphates.

DR. ROBERTS: Thank you, Dr. Durkin.

Dr. MacDonald, you are up next.

DR. MACDONALD: First of all, we were asked to pick from your menu in 1 H. So from that menu, I will select under Hazard Assessment Number 2, long term, research to develop and implement physiologically based PBPK models, which people have talked about.

And under food exposure, my favorites would be Number 1, series of sensitivity analyses for input parameters. And Number 3, detailed analysis of food exposure to identify major contributors to risk.

And in addition to that, I'll just elaborate a bit.

I think especially the discussion today has shown to me that we need a better understanding of the short and long term health risks from chronic and acute exposure.

And I think that this understanding will lead to better supported POD, perhaps even different PODs for different segments of the population.

And another point made earlier today, but sensitive, analysis for auto correlations in the activity diet and residue inputs to the model should be done. And if important, they will certainly emphasize that

we'll need more longitudinal data on these inputs in particular.

DR. ROBERTS: Thank you, Dr. MacDonald.

Dr. Harry?

DR. HARRY: I have a couple of brief comments. One is I really would like to encourage as much as you possibly can to back up the comments that were made earlier about trying to use the CDC data and THE NHANES data for evaluating and testing out what your exposure predictions were as to what is really there.

In addition to that, I'm not sure exactly how that data is, but if there is any way that a tweaking of that system could give you an idea of what coexposures might occur in people, I know you are getting the metabolites, but if there is any way you can pull out of there a little more idea of what actual in a way dose as we were suggested that dose was different than exposure, what actual mixture dose may happen of the organophosphates. If that is a source, it would be great, or any other human data that we might have for that.

Just encourage going after that a little bit more.

The other one is there has been a number of suggestions of doing modeling of your lumpy versus peaky exposure curves.

And while it is really nice to model and while it is really nice to have the pharmacokinetics, if we go into the neurotox endpoints of

those things, there is a lot of other dynamics that are going to be playing a role in recovery and that type of aspect.

It would be nice to have some experimental data to back up what predictions you might have if you start to model.

So if you had animals that were at a steady state like subthreshold steady state, do they actually respond differently to a peak than a naive animal. So does the exposure history do that.

And I don't know if you already have that data or not, but it seems to keep coming up as a difference. It would be nice experimentally to know if in the animals there really is a difference with the exposure history if it influences the response.

It is not going to be an easy thing to design and not kill an animal, but to try and get a feel for whether it does. It might give you a little handle, at least a little direction about what might be the most important one of those multiple exposure dynamics you could look at or at least to test back out your modeling.

As this will be opened up for general comments after this question, I know that there are a number of thoughts running around, I would like to take this opportunity as it goes on exposure assessments only, is that -- and it may be that the organophosphates and the use of them is different. So forgive me for that part of my naitivity if I'm

not sure about that, but we talked about institutional, and we talked about that in the form of schools and day care centers. And we have talked about some other studies that were being done. This is really sort of bad to say, but the oldest age we heard was 56.

I would like to argue that we have two extremes of susceptible populations. And it is not just the children. And it may be that the reason that the elderly have not had quite as much visibility in this is that they don't have their parents around to protect them as their children. So they don't have that group.

But you have as vulnerable a population, as dependent of a population on others on an environment and somewhat as trapped a population within their actual environment whether it's a nursing home or it is just their home type thing.

So I really would hate for that population to get lost in here. It may be that the strategy is that if we protect for one susceptible population, that that should cross over to another.

If, however, we start to think about nervous system effects, the dynamics of why they are susceptible are very different. And you may not be doing that. I just, since we continue to come up with children, and I know that that's a focus of this exercise, I would just like to take my soap box as the people eating the home grown foods that we also

think about the entire population -- because it is a public health, and that we don't give the appearance that we're looking at social impact so we're concerned about people under 50 or children that we would have a long term as in length of time social impact that we look at the whole population.

DR. ROBERTS: Thank you, Dr. Harry.

Dr. Adgate?

DR. ADGATE: Coming at the wrong end. I don't have a lot to say, other than I concur. And I agree with the point just made about the elderly.

One thing I noticed in looking at a lot of these, your charts, I was interested to see that I think they go from age 50 to 110, which was an interesting -- I don't know if that was on purpose or not. But I was intrigued by that when I saw it.

I have nothing else to add.

DR. ROBERTS: Let me, then, open it up to other members of the panel who may also have their views about what the most appropriate next steps are.

Dr. Richards?

DR. RICHARDS: Even though it appears to be a relatively unimportant pathway, I guess I better stick up for water here.

I wanted to comment just briefly on the list of items that's there under issues to deal with for water and suggest a few others.

The first one, I think, is an interesting one. It deals with the assumption that the applications all come on the same date and what impact that has on the assessed concentrations. And I think it is one that is worth exploring.

Clearly, it is going to lead to a higher concentration on some given day that's a response to that integrated, sort of simultaneous application.

But the difficult question is how is that going to relate to the timing of the next event to move this stuff. And that's going to be a stocastic question that is going to play itself out in the interplay between those two variables.

And I think, therefore, the conclusion about what impact that has on the overall results is really unclear and deserves what should be a fairly simple and sort of a kind of sensitive analysis. But it should be pretty easy to do.

There is a question in here about the proportion of the model residues that are or would be below detection limits of monitoring. Certainly worth looking at.

I imagine it will be a fairly good percent. Maybe as many as 40

or 50 percent. Maybe even higher. But I also suggest it's probably not going to have any important impact on the outcome because those concentrations are so low that not really having much of an impact on overall exposures.

Certainly, one of the things that we have identified the need for throughout this whole section is sensitivity analyses of various sorts.

And you list in one of the questions several that would be appropriate to do.

The one that I think I would add to that that might be the most useful would be some kind of an attempt to look at the possible impact of spatial heterogeneity within the region on the simulation results or the possibility that by having a place where you have concentrated use, quirky meteorology, whatever you want to pile together in that one local area that you would actually find that your supposedly worst case scenario is not protective of an area like that.

I think that's worth looking into in some more detail.

In terms of possible needs that aren't mentioned specifically, I think one of the things that would probably bear more useful information in several of the points you have actually listed would be developing the capability to create realistic simulations of concentrations in rivers and streams.

As it is now, you can only look -- you sort of used the reservoir as a surrogate for those. And it is not a very good surrogate in some respects.

So that is something that would be -- seem to have priority for development.

Another thing that several people in the water group are concerned about is the incomplete dealing with the degradates, particularly the ones that are produced in the treatment plant. And something needs to be done to address those.

And I guess the final thing is I guess I would put in a plug as Dr. Hattis did for what we can call a longitudinal study, I guess, and some long term detailed monitoring so that we actually have the data to look at the simulations and see how they work out.

That will only cost a few billion dollars a year.

Thank you.

DR. ROBERTS: Other suggestions?

Dr. Adgate.

DR. ADGATE: Just one thing I forgot to mention or the question I was going to ask, I notice the agency was asking about specific advice about prioritizing these lists that are presented.

And at least for the residential exposure part, a lot of what is

here, there are several points that allude to sensitivity analysis. And I think that's key.

And I think you have heard the other answers so you can infer them from our comments about certain conditional probabilities over time in longitudinal versus cross-sectional variability estimates.

DR. ROBERTS: Yeah. I agree, Dr. Adgate. I was going to mention that myself.

There are so many different kinds of data that you folks need. There are so many needs. And obviously, I think the best way to prioritize that in some respect is through sensitivity analysis.

I know that you folks are actively working on that. I guess we would expect you to be guided to a significant degree by what that sensitivity analysis tells you in terms of what the most eminent needs in terms of data might be.

Dr. Bull?

DR. BULL: I have not too much to say. But I did want to -- first of all, I was going to reinforce a couple points at least that Dr. Richards made, particularly about the steam. Because I'm not convinced that one shouldn't at least track these more flash -- what you might call flashy events that might occur in exposure instead of pesticides.

It may not -- and particularly the OPs because of the nature of the beast.

But if for no other reason, to know how often that might be encountered. There are places where that could be more important than others.

But the thing I would like to kind of come back to, because I think it is kind of the -- there is one thing -- I'm a toxicologist, so I have certain kinds of worries that other people might not have.

But one of the things that bothers me a little bit about focusing so much on mechanisms, what we perceive as being mechanisms of action, we have at least two groups of chemicals -- mechanisms that we're worried about -- because sometimes we lose sight of the other things.

And one of the -- and this has come up, and maybe not so explicitly stated as it should be, is that there really is a straightforward thing, this is a simplification of trying to determine what toxicities arise from cholinesterase inhibition or others.

Because you test a series of 10 compounds and they all inhibit cholinesterase to the same extent. And one compound doesn't give you the toxicity. Obviously, it is associated with something else.

And we tend to be lumping things. The endocrine assumption

thing is somewhat the same thing. You saw how the National Academy was really put off by that terminology. That was the reason, because you don't -- just because something has a property, the toxicity you worry about is not necessarily expressed by that mechanism.

And the cholinesterases are specific for -- the organophosphorus compounds are not specific for cholinesterase. That has been known for 40 or 50 years. They affect almost any hydrolase, however named, that has a serine hydroxyline (ph) active site.

So there is a lot of possibilities for other things to happen.

And I just get worried that we decide the only thing we need to focus on is cholinesterase and we don't need to do reproductive and developmental toxicities that may have these compounds that may have nothing to do with the cholinesterase activity.

I didn't hear that said by anyone else, so I thought I would say it.

DR. ROBERTS: Let's perhaps wrap up our discussion on this particular question. And we can perhaps get into some other general issues.

Are there anymore suggestions on next steps? Priorities for next steps?

I would have to say I think there have been a number of excellent ideas. I didn't hear a single suggestion that I disagreed with.

I think the issue obviously for the agency is priority. There were several people around the panel that echoed the desire to do some ground truthing for the model by comparison with human data wherever possible.

And I think that I guess that would emerge sort of as a priority based on the frequency of mention if for no other reason.

And the sensitivity analysis, I think, in terms of data for specific model components would be very important in terms of guiding the agency in terms of prioritizing those things.

Any other comments from panel members on this question before I open to general issues?

Before we move on, would you like any clarifications on our responses to Question 2?

DR. DOYLE: No. No particular clarifications. Just I would like to point out that we agree with a number of the -- well, all of them.

We have actually started some work on a number. We do have a schools project going on to try to get a handle on that.

We have a project to look at urban rural interface and try to

determine the magnitude of that population.

And there are a number of others that we have started. Certainly, not the breadth that is here, but we appreciate your input.

DR. ROBERTS: Thank you.

Let me then, as promised, open this final part of the session to discussion among panel members about issues that were not raised previously because they weren't part of a question or more general in nature.

I know that some panel members would like to discuss perhaps the endpoint and the appropriateness of it. There is perhaps some interest in discussing some margin of exposure issues as well.

So let me just open it for discussion. Let me just ask the panel, though, sort of to minimize sort of ping-ponging among topics. If someone brings up a topic and we have some discussion on it, let's go ahead and bring that to some closure to the extent that we can before we take up another one.

So who would like to start things off? Dr. Durkin.

DR. DURKIN: Thank you. I have two topics. And I would like to bring up the more minor one first. It is actually almost an improvement. I almost tried to sneak it in. It is really too to revisit an issue that we talked about on the first day.

And that is the issue of combining the studies. My understanding of what you did is that you took all of the studies that had been submitted to you by registrants that had been "accepted."

And then my understanding of what is accepted is it follows the protocol that at least was specified at the time of submission. Someone reads the study, they do a DER, data evaluation record, and it gets marked acceptable.

Then you turn that over to your statistician who plugged it in and came up with the dose response assessment. That's what I think happened.

The only thing that I would suggest, because I think we all nodded our heads and said, that's fine, and it might be fine, but I did want to open the discussion up to revisit that issue, because I have talked to some of the staff people here, and as a risk assessor, the one thing that I would intuitively recommend is simply that when you have a multiple number of studies, and your general expectation is that they all really ought to represent the same thing, perhaps follow approximately the same dose response assessment and you plan on plugging them all into a model at one time, I didn't hear any discussion of judgment, because it is not uncommon if you have, let's say, three or four studies on either kinetics or toxicity to have maybe two or

three of them hang together very nicely, one study is way off base.

And even though that way off base study could be acceptable in terms of your data evaluation record, it is the kind of thing where I think you can look at it and either using statistical wizardry or judgment say you are better off dropping that study.

And I know that's a little bit messier, but I would like to recommend that at least you think about it and perhaps hear what other panel members think.

DR. ROBERTS: Dr. McConnell, not to put you on the spot, but I think that was an issue that you had broached on the first day as well.

Comments by other panel members on the idea of sort of inserting another -- a layer of judgment in terms of evaluating the data?

I'll go on the record as concurring with Dr. Durkin. I think that there may be some desirability in that. I think that -- if you look at enough of these things, all studies are got created equal.

I realize the agency might want to -- might be reluctant to do anything that might suggest bias in terms of evaluating the data.

Obviously, if they threw out data sets, that should be accompanied by some explanation of why a study's value was

downgraded or that sort of thing.

That should be a fairly transparent process that people could look at and see and agree or disagree with the agency.

But I think the opportunity to exercise some judgment would be perhaps a good thing.

DR. DOYLE: Actually, during the initial pass instead of evaluating the tox data, we did start a process such as that.

But we found that we were constantly throwing out more and more data and became concerned about the extent to which our criteria were not appropriate, too rigorous, how ever you would like to define it.

So we then reversed the process and began reinserting them because we weren't certain that we weren't biasing the analysis in just the opposite way of eliminating too many. Because you can significantly change the outcome that way.

So we decided to err on being inclusive rather than too exclusive.

DR. DURKIN: If you look at statistical methods, you might use a more objectively determining -- if you have four studies and one of them appears to be way off base, I believe, again this is not my -- I'm still not a statistician, but I think that the wizards can tell us that there

are indeed ways to do that very objectively.

What I'm getting at here is we have a tremendous amount of uncertainty in risk assessment.

And this is one way to maybe take off some of that burden in a very objective manner.

DR. ROBERTS: Any other comments or responses?

Dr. Hattis, then Dr. Harry.

DR. HATTIS: I guess I should defer to the real statistician down the table there. But I just would urge that one -- if you use a statistical, a purely statistical criteria, you are correct that there are statistical criteria floating around there, sometimes people choose relatively liberal criteria for defining what is a "outlier." And sometimes people are relatively conservative.

I worry unless when it is pretty damned conservative. One such criterion is by saying the outlier study has to be more than X standard deviations from the mean determined by the set of other studies.

And I would just suggest that X be in a pretty convincingly large, you know, four or five or something of that sort, otherwise, one does get into the difficulty that you have thrown out in some sense real cases.

DR. DOYLE: Yeah. One of the concerns that we had we did

look from the standpoint of I think goodness of fit. Is that correct?

One of the things we found was that some of our toxicologists disagreed with which studies actually were more reflective of what was going on.

They felt that the goodness of fit test, they disagreed with the outcome of some of those tests that were conducted. So it put us in a bit of a quandary that in fact their judgement in interpreting the data did not match what statistical methods were used.

DR. ROBERTS: Dr. MacDonald, did you have a comment?

DR. MACDONALD: I would be pretty careful about using statistical goodness of fit methods in particular. It just means that the smaller samples will show better fits and the large samples will show bad fits.

I think you have to use more than just looking at the numbers because you could easily get three bad studies and one good study.

And I wouldn't even guaranty the one good study was the outlier. It is not an easy problem. You need an awful lot of judgment.

DR. ROBERTS: There may be attributes of the study that as you say lead you to conclude that the one study is in fact good and three of them are bad.

I agree that it is not an entirely statistical decision. But I sort

of sense that some people, the panel is sort of opening the door to that possibility of exercising that judgment.

But obviously recommends that it be done very cautiously.

Dr. Heeringa?

DR. HEERINGA: Actually, Dr. Durkin and I had this discussion yesterday. I think as a statistician you are trained never to throw away data. In fact, there is information even in bad data. It may be about the reliability of the test procedure, about the types of errors you can commit in conducting these tests or missing variables that are present in one study and not in another.

So I think when we talked about it, I tend to be very conservative about throwing out data. And I also agree with Peter that simple statistical tests on distributional fit tend to be overly powerful for any sort of reasonable sample size, and probably not very reliable when you get to be too small.

I think some of it is sort of interocular tests where you just look at things and then investigate.

And I had one example that I would point out as a starting point. That is the dose response curves that are fit to phosmet.

If you look at the curves that are produced in the document or on the CD, you have one sort of dose response curve that seems

reasonable to me.

And that is it is -- at the origin in terms of dose, it has a very low suppression of cholinesterase activity.

A second study apparently without even dosing these animals the curve is already suppressed 40 or 50 percent or at least at really very low doses. It literally has the appearance of two different curves to me. Not even sort of a normal scatter.

The first thing that occurs to me in that particular case is that something happened in one of these studies or the conditions are so radically different in one of these studies that it really shouldn't be combined.

I only pick on that as sort of the extreme case that I noticed in looking at these as to the type of thing that --

What you do find when you look at the data is that the main OPs, particularly methamodophos, that these curves and these studies are all actually very consistent. And as we discussed the other day, I think are generally amenable to this mixed effects model that is being fit.

What happens when you only have two or three studies, I don't think you can -- as Peter says, you can never tell which one is the odd person out here.

So I think we need to be cautious on this. But I think it is something worth revisiting and clearly in cases where it can be either because the studies are extremely old or the conditions under which they are conducted can't be validated or verified, I think it is worth considering at least refitting the model with some outliers removed to see what impact that might have.

DR. ROBERTS: Thank you.

Dr. Harry.

DR. HARRY: Just one quick one to go off on those. A comment I was trying to make the other day is especially when you are trying to equate potency across chemicals across studies that you really have to be careful to try to ensure that everything is as equal and as precise and as sensitive as it can possibly be in there.

And I don't know about your practices, but is this an opportunity like if you are going back through these studies and you are finding the ones that you disagreed on or the interpretations or things there, is there any mechanism that the agency has to offer additional guidance?

I know the guidelines are set down a certain way. But is there any guidance that is offered to people submitting the data as in how to run, you know, what works best as in running these assays or anything

like that or is it just sort of set up to how they design it?

DR. DOYLE: Pretty much the testing guidelines at this time refer to study design more than conduct.

I know that the conduct of cholinesterase evaluations has been discussed a lot of times at various, I think, SAPs even.

One thing that we are looking at is testing guideline revisions. And some of the issues that we do want to consider are the very sorts of things that are coming up here about how our studies are not meeting our needs.

So I think this is very helpful.

DR. ROBERTS: I think we have just about reached convergence in terms of consensus on this issue.

Let's go ahead and move on to another one.

Pat, do you want to bring up your Number 2?

DR. DURKIN: Yes. My Number 2 is a biggy for me. And I really think we need to get some response from the committee here, because I misunderstand.

Shortly before coming down, I received a packet from you folks, some comments from Brian Demente. Brian had been through the wars with malathion. Brian and I are both veterans of a malathion war because I have recently been through a very detailed risk

assessment for USDA on malathion.

So brian and I may both be suffering from the same disease.

Having said that, I came down here and Dr. Sass kind of reinenforced my malady. Where are the kids here? This bothers me. It bothered me before I got anything from you.

And what is concerning me here, like, if the story is that we're going to address kids at some other point, I'll say that's fine.

But don't give me margins of exposure for kids. Because you are basing that on exposure to the kids, which is good, and we have talked about that, but then the relative potencies that you are coming up with are based on adults.

And I will contend strongly that that is absolutely incorrect and wrong.

For some of the OPs, malathion is a very good example. It is not very toxic to adults. It is substantially more toxic to neonates. So I am a little angst, in fact I'm very angst, that you present that assessment prior to coming up with a separate set, which I think you need, totally separate set of relative potency parameters for neonates and apply that to the exposure assessment for kids.

I think that's the only rational way to go about this.

For some of the OPs, I know it does not make a great deal of

difference. For others it does. And that's why you have to consider kids as a separate group.

Right now I think the margin of exposure that I get for kids is a margin of exposure for very small adults.

So that is something that I think does have to be addressed as part of the revision to the document. And I think it is a substantial assessment unless I totally misunderstand things.

The one minor point that I'll make, though, and Dr. Demente made this as well, and I want to endorse it, when you did your 1998 assessment, I believe, on the application of the FQPA uncertainty factor, you based it largely. You covered all of the OPs. And that's very commendable. You based it, I believe, exclusively on studies that have been submitted to you for registration.

I would encourage you, because I know it makes a huge difference with a malathion, I would encourage you to look out in the open literature, because we have known for a while that malathion is more toxic to neonates than to adults and it's not an uncommon pattern with OPs, although it is not a universal pattern.

It is tricky, and I think it has to be handled on a case-by-case basis. So that is my strongest most vigorous criticism of your effort here.

And I would like to hear some consensus from the committee. If I am just a victim of my malathion risk assessment, please just wrap me up and send me home.

But if I am correct, and this is a very, very important issue, then I think the committee has to very, very strongly and clearly state that this cumulative risk assessment will be in no way ready for a final review until those differences in sensitivity are quantitatively addressed and put into the risk assessment.

DR. ROBERTS: I would like to let Dr. Doyle respond before we get more input from the rest of the committee.

DR. DOYLE: There are several components to what you said, of which I'll try to march through at least as many as I can remember.

First of all, I would be interested in -- we are doing the rat on malathion now. And I would like to see a risk assessment, if you can share it.

Second, is we, I don't know the year, but a DCI for something called Developmental Neurotoxicity Study was issued for all the OPs.

We are in the process now of receiving those. We have not received many, but we have received malathion among the five that we have. And we are aware of the issues around that.

One of the discussions that you haven't heard or seen in the risk

assessment is what the appropriate MOE will be because of the FQPA issue, the relative sensitivity.

So we have not yet frankly finished formulating how to do that.

We have guidance that we drafted that were put out that is generic. We are also putting out a specific statement the next several two or three months, by the next two months, I guess, is what we have left to do this, on how we propose to deal with the FQPA issue based upon what data we have in, which right now is, like I say, a total of five neurotox studies, including relative sensitivity data for cholinesterase inhibition in the brain and how we hope to factor in that and our lack of understanding for other chemicals.

So we have not overlooked that, but we cannot tell you yet what approach we will take. But you will be certainly free to comment at that time.

We also have not yet determined a number of other issues around how to deal with special subpopulations. So we do appreciate that children are not miniature adults. But we also are limited in what data we have available. And we have to figure out how to apply it appropriately. There is no pretence.

I'm very well aware of Dr. Demente's comments. I received copies of them myself. And I have read them and I understand them

quite well.

But we don't yet know how best we can address that. That's under development.

DR. DURKIN: May I put a footnote in in response?

DR. ROBERTS: That's fine.

DR. DURKIN: One of the reasons that I am -- we're all concerned about kids.

The rest of the world looks at you for guidance here. And in my risk assessment for USDA, which I will leave with you, they elected to defer any decision to your analysis, which I support, but I am just trying to underscore the importance of how you handle it is going to make a huge difference and appropriately so to how it is handled by the rest of the government.

DR. MULKEY: Maybe I could add one thing to what Beth said that might help clarify. As we have worked through each of these individual organophosphates, we have worked through this issue about the, what we call the FQPA safety factor, but the analysis of whether we think we have enough -- we have uncertainty about the differential impact on young, what information we do have, whether we believe we need additional safety factors, or, that is, we're aiming for a higher MOE.

So in addition to the work we will do in connection with this cumulative assessment, we are working through that for each of the individual assessments.

Malathion is one of those that we have not yet completed. And Dr. Demente is working, of course, he is one of our respected scientists, and he is working with us as we work through at that level as well as the issue regarding the cumulative risk assessment.

DR. ROBERTS: Thank you, Ms. Mulkey.

Dr. McConnell?

DR. MCCONNELL: Yeah. Maybe I can help Dr. Durkin here a little bit too.

Having chaired one of the meetings where this was dealt with, it was a conclusion of the science advisory panel, and I think the EPA adopted that, that the best place to bring in the differential potency between adults and children was, if you will, after the risk assessment had been done and you came up with a number.

Then you would say, now, based on your information, we need to further protect by lowering that number for children.

DR. DURKIN: Lowering the MOE.

DR. MCCONNELL: The MOE for children. Because if you start doing it during the process, it becomes quite complex and you

lose it in the mix. And it gets multiplied three or four times during the exercise in addition, that it was just cleaner to do it -- you do the whole risk assessment and then you decide, now, I'm going to evaluate whether there is a unique problem for children or not.

DR. ROBERTS: Did you want to respond, Dr. Durkin?

DR. DURKIN: Yes. That approach works if the difference in sensitivity between the neonate and the adult is consistent across chemicals.

Regrettably, with the organophosphates, as far as I can determine, now I am not a total expert on DOPs, but I believe that there is not a consistency.

So then it depends upon the mixture that you have and a uniform approach to saying we're just going to lower the MOE may not be appropriate.

DR. MCCONNELL: This was for individual OPs.

DR. DURKIN: Oh. For individual OPs, it is fine. But for the cumulative risk assessment here I think it doesn't work.

DR. MCCONNELL: The second question I was going to ask of you, when you were talking about relative potency, I assume you are talking about relative potency in terms of children versus adults.

DR. DURKIN: Right.

DR. MCCONNELL: You weren't saying that if I study a malathion in an adult rat and I give it a one X and I study another OP in an adult rat and it is twice as potent that you would expect that to change those relative potencies in the neonate?

Is that what you are suggesting?

DR. DURKIN: Yes. It could.

DR. MCCONNELL: Anything can happen. But I mean --

DR. DURKIN: I believe that that is known to happen, that for some of the OPs there is very little difference. For other OPs, there is large difference in relative potency between the child and the adult.

DR. MCCONNELL: No, no. That wasn't the question. The question is if a given OP A is more toxic than B, are you suggesting that, in the neonate, B would be more toxic than A?

That's relative potency too. But it's a different kind of relative potency.

DR. DURKIN: I don't really know. I think that it could be.

DR. MCCONNELL: You think it could.

DR. DURKIN: I think it could. And I think malathion might present an example. But I honestly am not -- I cannot come up with an example.

DR.L MCCONNELL: Malathion versus which other OP, would

be my question.

DR. DURKIN: I don't know. I would have to look -- I think one might possibly be methamodaphos, but I'm not sure. I would have to look at the data.

And I do agree that we have limited information. And I fully understand that.

What greatly disappointed me in the document maybe was at least the really lack of any acknowledgment of this issue. And that, I think, could be relatively easily corrected.

DR. ROBERTS: Dr. Doyle?

DR. DOYLE: I think you will find that there will be a full discussion of that in the June document.

However, at this time we have the difficulty that not having made the decision we wanted to provide the intersection of the exposure and the toxicity data for evaluation and not hold that back waiting for the decision on how to handle special sensitivity.

So I think that that was a deliberate omission on our part. Not that we don't realize this error, but we felt that we were not ready to release it.

DR. ROBERTS: Dr. Harry has been waiting patiently to weigh in on this issue.

DR. HARRY: I think in a way you answered some of it that you are going to be putting this out a little bit later.

But one of the questions was, and I think you are going to find it a little more complicated, but I have one, first question before I get into that is, you are going to look at each of the individual compounds, and you do have the enzyme inhibition data on these compounds. You said you have five in now.

When you go to look at a cumulative on those, are you also assuming that it will be this enzyme inhibition that will be a common mechanism that you can use at which to look at potency?

DR. ROBERTS: Dr. Doyle?

DR. DOYLE: In this case, yes. We're going to continue to use -- our common mechanism here across the board is going to be cholinesterase inhibition.

That does not say that we do not realize that OPs in some cases do other things. And they in many cases do a surprising variety of things, everything from cancer to developmental effects.

But for this particular exercise as defined in the act itself, we are focusing on this particular mechanism.

DR. ROBERTS: Dr. Harry?

DR. HARRY: Then I have a couple other questions. And they

are more -- you don't have answers for them, but just to keep them in mind. And a lot of them have been raised in the sense that there are other components of toxicity that can happen that are not necessarily related to this process.

The effort that the agency came up with, as well as outside academic researchers, to identify that this could be a common mechanism of action is a lot of work that was put on adult animals. A lot of the characterization of the adult versus the steady state.

What I would like to ask is are we proposing to skip that effort in the developing animal? I mean, is the acute the same as it would be in the adult? Is the steady state reached at 21 days? Is this being done under the EPA developmental neurotox protocol dosing regiment as is in there or is it direct dosing to the pups.

There may be a lot of things you are going to have to look at before it is even worth thinking that it is going to be a common mechanism of action that would be accepted.

You can do an awful lot of work and come back and say, we really shouldn't have done this. We lumped these together incorrectly. And given that you have a number of questions that are being raised now about which chagrin after everything you went through to get this, that it may not be the right endpoint. Then you are going to have

to go through those hurdles again developmentally and not just make a tacit assumption that it's going to work through there.

I think you are going to find it a lot harder than what you really want it to be or probably as hard as you expect it is going to be.

DR. ROBERTS: Dr. Doyle, do you want to respond?

DR. DOYLE: I think that she summed up a lot of issues.

Part of our limitation now again is we have limited data. And we have mixed protocols. You have identified a number of points. Yes.

But again, I just can't really tell you how we're going to come out with it.

DR. ROBERTS: Other panel members with viewpoints?

Dr. Hattis.

DR. HATTIS: One way in which you could get a lack of parallelism in the relative potencies between at least neonates and adults is in fact if a substantial fact -- modifying factor for the toxicity is in fact detoxification by specific liver enzymes.

Because some of the P 450 enzymes in particular seem to turn on in the first few months of life but after birth, so that half lifes of some chemicals -- in fact half life for many chemicals, many drugs, in neonates can be of the order of two to fourfold larger than they are in

adults because of the immaturity of that metabolism system.

So chemicals that are detoxified substantially in the liver versus those that aren't could well have a lack of parallelism in that systematic way.

DR. ROBERTS: And the ontogeny of P450 development is different in rats than humans. Actually, substantially. So that's a further complicating factor, unfortunately.

DR. HATTIS: Okay. I don't know in rats at all.

DR. ROBERTS: Other comments?

Dr. Harry?

DR. HARRY: Just one more to put as a red flag for your comparison, because I'm not sure that it's appreciated by everybody except the ones that are working with the data set, is that your adult neurotox test battery is actually a relatively crude battery.

The developmental, it is not only supposedly looking at a more sensitive organism and time point, but it is also looking at it much more in depth.

You actually have some learning tests and measurements in there, which you don't have in the standard adult battery.

So as you are looking at that, if you just say you have a positive response at a lower dose on the development, it is not necessarily

going to mean that they are more sensitive. You have a sensitive test battery to look at.

So a lot of that is going to be presenting exactly what you are comparing. And they are going to be different. It is not going to be a tacit assumption that you -- you may just be picking up something because you have more sensitive tests to pick it up.

DR. ROBERTS: Are there any other comments by panel members on this particular issue?

I don't see any.

Are there other issues that panel members want to bring up?

Dr. Harry, are you signaling me?

DR. HARRY: No. I'm looking around.

DR. HATTIS: I just wanted to say that I had -- I thought that the EPA staff did a wonderful job on the expanded model for trying to assess nonlinearities at intermediate lower doses.

I thought that was entirely an excellent implementation of the mechanism-based understanding that we had. I was not here on the first day, so I thought I would insert that here.

DR. ROBERTS: Thank you.

Any other issues to be raised by panel members?

Are there any clarifying issues that the agency would like to

raise with the panel while we're all here?

DR. DOYLE: No. But I would like to thank you all for your discussions and your inputs. And I think we have a lot of work ahead of us. If you don't see these show up in the June documents, we certainly hurried them and they will show up in subsequent rounds. Thank you very much.

DR. ROBERTS: Thank you, Dr. Doyle.

I would also like to thank the agency for some tremendous presentations trying to clarify a lot of information for us. You did a great job.

I would like to thank the panel members for coming, for being very prepared. We had some excellent focused discussions.

I would like to thank Dr. Kendall in his absence for chairing the first two days and getting us to the point where we could complete our agenda today.

And, of course, I would like to thank the SAP staff for the tremendous amount of work it takes to put one of these sessions together. They work behind the scenes. They do a lot to make this all very possible.

Ms. Mulkey, did you want to say something?

MS. MULKEY: I would like to make some very brief remarks.

I would like to thank on behalf of the agency the panel for its work. I would like to thank you for the balance you gave between offering us advice that we can practically use within the practical limitations and asking us to reach beyond that.

I will say that if we had sat here this time last year and heard these suggestions, I think we would have felt overwhelmed.

The distance we have come has given us a lot of confidence about how far we might yet eventually be able to go. But we also appreciate your awareness of the distance we have come and the practical place that we are.

So we found this constructive, helpful. And to the extent that your report can make it clear the kinds of things you are saying to us about priorities and near term ideas, that is particularly useful to us as we face the next few months.

Thank you again.

DR. ROBERTS: We will do our best on the report.

Also, I neglected to thank the public commenters. They provide valuable input for SAP. We appreciate their input and suggestions as well.

Is there any other business or comments anyone on the panel would like to raise?

None. This session is closed. Thanks again.

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[Whereupon, at 5:05 p.m., the meeting concluded.]

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