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FIFRA SCIENTIFIC ADVISORY PANEL (SAP)
OPEN MEETING
FRIDAY, DECEMBER 3, 2004

N-METHYL CARBAMATE CUMULATIVE RISK ASSESSMENT:
STRATEGIES AND METHODOLOGIES FOR EXPOSURE ASSESSMENT

VOLUME I OF I

Located at: Holiday Inn Rosslyn at Key Bridge
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Arlington, VA 22209

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C O N T E N T S

P R O C E E D I N G S

DR. HEERINGA: Good morning everyone, welcome to today's December 3rd session of the FIFRA Scientific Advisory Panel on the topic today of the N-methyl Carbamate Cumulative Risk Assessment, Strategies and Methodologies for Exposure Assessment. I'm Steve Heeringa, a member of the permanent FIFRA

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SAP who will serve as session Chair today.

I would like to begin our session by introducing the members of our expert panel that we've assembled and I would like to begin on my right with Dr. Ryan, please, if you just give your name and affiliation and area of specialty.

DR. RYAN: My name is Barry Ryan, I'm from Emory University, Rollins School of Public Health, Department of of Envoronmental and Occupational Health

and my specialty is in environmental exposure assessment.

DR. HARRY: I'm Jean Harry from the National Institute of Environmental Health Sciences, I'm head of the Neurotoxicology Group.

DR. WHEELER: Michael Wheeler, University of North Carolina, Department of Pharmacology and Nutrition.

DR. KEHRER: Jim Kehrer, University of Texas at Austin, free radical toxicology and apitosis signaling.

DR. FREEMAN: I'm Natalie Freeman, University of Florida College of Public Health and Health

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Professions and College of Veterinarian Medicine, exposure assessment.

DR. MACDONALD: Peter MacDonald, Professor of Mathematics of Statistics at McMaster University in Canada, a general expertise in applied statistics.

DR. HATTIS: Dale Hattis, Clark Univeristy, risk assessment modeling with emphasis on issues of variability and uncertainty.

DR. REED: Nu-may Ruby Reed, California Environmental Protection Agency, pesticide risk assessment.

DR. EDLER: Lutz Edler, Biostatistics Unit of the German Cancer Research Center and specialties are kinetics, modeling, and data analysis.

DR. CORCORAN: George Corcoran, Department of Pharmaceutical Sciences of Wayne State University of Michigan, mechaninisms of cell death in the liver is my specialty.

DR. SOHN: Michael Sohn, Lawrence Berkeley National Laboratory Indoor Environment Department, my speciality is exposure assessment modeling and data analysis.

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DR. FISCHER: Larry Fischer, Michigan State University, environmental and biochemical toxicology.

DR. LU: Alex Lu, Emory University Rollins School of Public Health, I'm interested in developing biomarkers for pesticide exposure assessment.

DR. HANDWERGER: Stuart Handwerger, Univeristy of Cincinnati, molecular and developmental endocrinology.

DR. PORTIER: Ken Portier, University of Florida Department of Statistics, I have interest in statistical issues and risk assessment.

DR. CHAMBERS: Jan Chambers, College of Veterinarian Medicine at Mississippi State University, pesticide toxicology with emphasis on neurotoxicology and metabolism.

DR. ISOM: Gary Isom, Purdue University, I'm a neurotoxicologist, my research interests are in molecular mechanisms and neurodegeneration.

DR. HEERINGA: As indicated earlier I'm Steve Heeringa, the Institute for Social Research at the

University of Michigan, I'm a statistician with an area of speciality in population-based research design

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and no specific expertise today except I'm charged with chairing this meeting.

I want to start with just a quick comment to everyone, part of my job as Chair is to make sure we have ample time for discussion and all of the ideas, all of comments, all of the points of clarification can be obtained or made, and we face a little bit of a challenge today, it's the end of a week, a long week for many of these panel members who are seated here. I know that a number of them have flights and want to make it home tonight, so we will be pressed at the end of the afternoon, and so I am going to try to keep things on track with our agenda and I hope that you'll bear with me on that.

I don't want again to short circuit anything that needs to happen here today, but let's please all keep focused on that because you know from past experiences the worst thing that could happen is we could spend a lot of time in early phases only to wind up pressed at the end and I think we certainly want to sort of balance our time allocation across all the phases of the agenda today.

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At this point I would like to turn to the designated federal offical for today's meeting, that's Mr. Joseph Bailey of the FIFRA SAP and see if he has specific comments on the meeting and the meeting proceedings.

MR. BAILEY: I'm Joe Bailey, I'm the designated federal official for today's meeting. And as the designated federal official I serve as the liaison between the panel and the Agency on all issues related to this SAP meeting. The FIFRA SAP is a federal advisory committee that provides independent scientific peer review and advice to the Agency on pesticide issues as they relate to proposed regulatory actions that may affect human health and the environment. The SAP only provides recommendations and advice to the Agency, ultimate regulatory decisions are left up to the Agency itself.

With regard to ethics and selection of the panel as the designated official one of the critical responsibilities is to work and ensure that all ethics regulations are met. To that end we have asked all of the panel members to fill out a standard form of

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ethics requirements and we have reviewed that form to make sure that all of the ethics regulations have been met, along with the Deputy of Ethics Office or for the Office of Prevention Pesticides and Toxic Substances along with our Office of General Counsel have reviewed these forms to make sure that all requirements are met.

As part of the meeting since this is a

meeting under the Federal Advisory Committee Act certain regulations are required, it is a public meeting, we have time set aside this morning for public comments and I believe as of right now two individuals or groups have identified themselves as public commenters. If there's anyone else in the audience that wishes to make public comments today either let myself or any of the other scientific advisory panel staff members know that you would like to make comments. And if you haven't made prior arrangements to make public comments we ask that you restrict your comments to five minutes during that comment period today.

There is a public docket established for the

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meeting, it contains all of the background documents, all of the presentations that will be made today will be put in that docket and they should be available within a couple of days. And the agenda that you have should list where you can get any of these dockets from either our web page or from the public docket .

Another requirement for this meeting is we will put out a report or meeting minutes after this meeting is concluded and we anticipate that that report will be available in approximately six to eight weeks after the meeting. One other thing I wanted to note, the handout, one of the handouts that you have for today, the front page is entitled EPA FIFRA SAP CRA Exposure Models, the rest of the pages in that handout have yesterday's title on it, so once you're passed page 1 don't let the title at the top of the page confuse you because it's the wrong title and the correct for today's meeting is CRA Exposure Models, all of the slides should be correct on pages 2 through 10, it's just the title at the top of the page that's not correct, we apologize for that. And that concludes my remarks.

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DR. HEERINGA: Thank you very much, Joe. One last minor administrative detail on my part, the proceedings today will be both tape recorded and transcribed and for the transcriptionist it is very helpful if when you approach the mike always use the mike to speak, that you state your name and affiliation so that she can pick that up and also that we have it on the recording if when we go back to know who has made which statements during the course of this meeting.

Thank you very much and let's move right into the main body of the agenda, again this morning I would like to welcome Mr. Joe Merenda who is Director of Office of Science Coordination Policy at the EPA, Joe might have a few introductory remarks.

MR. MERENDA: Good morning, thank you, Steve, welcome to the panel and the public participants. For those of you who are joining us this morning welcome and we very much appreciate you're serving on this

FIFRA Scientific Advisory Panel. For those of you who have been with us this is your second day and for a number of you for whom which this is your fourth day of service on the three FIFRA SAP's that have been held one after the other this week, you deserve the medal of valor for sticking with this.

As I have said at the opening of the other sessions this week, and I think it is important to highlight again this morning, within EPA the concept of transparent external rigorous and independent scientific peer review is very important to the way we carry out our activities. One thing that I haven't specifically mention in my remarks earlier this week but which the topic this morning particularly reminded me of is that since the 1996 passage of the Food Quality Protection Act EPA has been faced with a huge number of new significant scientific challenges, and the topic today is probably one of the -- an element of one of the most critical of those, the whole concept of cumulative risk and how to do very sophisticated risk assessments based upon that concept.

So we very much appreciate your contributing your expertise, your time, and your energies to supporting the Environmental Protection Agency and its scientific activities and I wish you well in today's deliberations. Thank you.

DR. HEERINGA: Thank you, Joe. Now I would like to turn to Randy Perfetti also of the EPA with the Health Effects Division Office of Pesticides Programs.

DR. PERFETTI: Thank you, Dr. Heeringa. Welcome to the panel and again thank you for sticking with us for this marathon week. I will keep my comments as brief as I can. I know that everyone in this room believes that physiologically based pharmacokinetic modeling is the future, it's the future of risk assessment and OPP is firmly committed to going down that path and implementing that methodology. It turns out however that we have picked a rather knotty plank to work with in this thing and this is our second conceptual meeting that we've had with you, we had one last year.

Today what we need your advice on, and we really do need your advice, is the way in which a lifeline model that generates exposures can be modified to feed into a PBPK model so that we can smoothly, not smoothly, but at least continue down the path of this very cutting edge part of risk assessment. Thank you.

DR. HEERINGA: Thank you, Dr. Perfetti. At this point I guess I would like to move into the opening remarks or statement of the goals and objectives for today's session and the presenters for

this will be Dr. Anna Lowit and Mr. David Miller of the Health Effects Division Office of Pesticide Programs.

MR. MILLER: Yesterday you heard as part of a separate SAP about an initial attempt and incorporating PK studies developed for carbaryl. Today we're going to move onto the initial phases of the N-methyl cumulative risk assessment into which we hope to be able to incorporate some aspects of the PBPK approach.

This is the second in a series of scientific peer views for the cumulative risk assessment of the N-methyl carbamates. The first was PBPK modeling for the N-methyl carbamates which was held back in December of last year, we have a third meeting

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scheduled for mid-February of 2005 that will cover hazard assessment, PBPK/PD modeling, drinking water models and a case study.

You received an attachment with your background material to this that explains a little bit more detail of what those different days will deal with and Anna Lowit in her part of this presentation will be discussing in a little bit more detail as well. As far as a time table I will just kind of give you a general idea of where things are in terms of a time table on the next slide. We anticipate a pulmonary cumulative risk assessment in the spring of 2005 as a follow-on to the case study that you'll be seeing in February. We expect a release of a revised cumulative risk assessment to the public in the winter of 2006, and then we expect a tolerance reassessment of the N-methyl carbamates by August of 2006 which we based in part on the results of the cumulative risk assessment.

There will be two basic parts to today's presentation, the first will be a background presentation by EPA, it will be a quick review of the

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background document you were provided as part of your package, it will be given by both me and Anna Lowit. Next there will be a presentation of the white paper by the LifeLine Group, presentation will be given by Paul Price, Chris Chaisson, Claire Franklin.

The objective of the current SAP review is to solicit comments on conceptual aspects of the exposure model and the exposure to PBPK/PD interface and linkages at an early stage of the N-methyl carbamate cumulative risk assessment.

The next slide presents a brief outline of what the first part of the presentation will cover. We will start with a real quick review of the EPA and LifeLine Group documents that were presented to you in your package. Next we'll cover the history and the background of cumulative risk assessment, things like the common mechanism group, common assessment group, cumulative mechanism group -- common mechanism group

and the cumulative assessment group, various ways to develop the scenarios as well as approaches to the cumulative risk assessment.

We will move onto general steps and

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cumulative risk assessment and then move on finally to N-methyl cumulative risk assessment time line. You received many papers in your package, the first and I have one slide on this and that's the EPA background paper. It gives you some historical background regarding the cumulative risk assessment, it covers the general framework for the development of the N-methyl cumulative risk assessment, it went through in a general way some of the procedures used to identify the N-methyl common mechanism group and cumulative assessment group, it describes anticipated next steps for the N-methyl carbamate cumulative risk assessment and then provides the regulatory context for the LifeLine Group white paper.

The second paper you received in your package was the LifeLine Group white paper. Again as I mention said before the LifeLine Group will be presenting this, it describes an approach to deliver appropriate exposure metrics to the PBPK/PD model. It discusses essentially modification of the current exposure information, and again they'll go into more detail on this, it talks about extending the software

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to provide additional pertinent information on individuals being modeled, it also goes into and defines the technical process by which information is transferred from the exposure model to the PBPK/PD model and there will be a number of questions that you will be asked about this.

I will just emphasize the approach is designed to be generic not model specific, this general information here can be applied to any and all models. Cumulative risk assessment, just kind of some slides on history and background, historically we focused on single pathways of exposure for individual chemicals, we did not consider historically exposure to multiple pesticides by all pathways and routes.

In 1993 the National Research Counsel came out with a report Pesticides in the Diet of Infants and Children, it charged a multichemical/multipathway approach, indicating essentially aggregate exposure, what was later termed to be termed aggregate, that is consideration of all sources of dietary and non dietary exposure, and it also encouraged as well cumulative risk assessment whereby an assessment of

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risks was done from exposure to multiple pesticides that act by a common mechanism of toxics. Several years after the NRC report the Food Quality Protection Act was passed in 1996, it requires EPA to take into account one setting of pesticide tolerances and the available evidence concerning the cumulative effects

on infants and children of such residues and other substances that have a common mechanism of toxicity, so it would essentially require to us to perform what before had NRC had indicated as cumulative risk assessment that's multi pathway and multichemical.

Following the passage of the Food Quality Protection Act OPP developed on the next slide guidance for documenting -- a guidance document for cumulative risk assessments under FQPA. It established the core principles for performing cumulative risk assessment and also developed tools for calculating multichemical and multi pathway estimates, risk estimates with an emphasis on the relevant potency factor approach that was used in the OP assessment.

The next slide kind of gives you a quick

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overview of some of the general steps outlined in OPP cumulative guidance. The first step would be to identify common mechanism effect in the common mechanism group, after that the next step is to identify the cumulative assessment group or the cag, that's essentially a subset of the common mechanism group on which the assessment, the cumulative assessment will be based. After that determine the relevant exposure scenarios and pathways for the chemicals in the cag, then consider the appropriate methods to conduct the cumulative risk assessment and then conduct the cumulative risk assessment. Anna Lowit will be talking about these latter two.

With respect to determining the common mechanism group, there was US EPA policy paper in 2001 that looked at structural characteristics and cholinesterase inhibition and various places that occurs, the conclusion of this 2001 policy paper was that the N-methyl carbamates were selected as a common mechanism group.

After this it is required that two select a subset of theses CMG chemicals as a cumulative

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assessment group or cag, not all chemicals grouped by common mechanism of toxicity should necessarily be included in a quantitative cumulative risk assessment is one of the things that the policy paper indicated. For example, exclude those chemicals, those chemical uses and those exposure scenarios and pathways for which exposure would be deemed and can be shown to be negligible.

We did this in terms of reviewing the OPP data bases to determine those CMG members that have active food or residential registrations or those that may have drinking water impacts and remove those chemicals that are currently undergoing phase-out or cancellation.

This is the list of chemicals that we have determined to be the N-methyl carbamate cumulative assessment group, these were published in February of

this past year of 2004 as a Federal register notice.
The next step is to develop exposure scenarios for the cag and what we do once we've defined the cag as we have what we do is use available information to develop these exposure scenarios, food

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they primary sources of information are USDA's Pesticide Data Program as well as FDA monitoring data, for drinking water it's a matter of looking at use/usage information, labels a well as prism exams and the ground water models, and on the residential side it's a matter of looking at use/usage information as well as labels.
That's the end of my part of the presentation here, Anna will be continuing next with the next two bullets.
DR. LOWIT: Before I go through the rest of the slides we wanted to take a minute as we sort of move into from the steps that are complete or that we've done before and to talking about the methods and sort of segue into today's presentation just to give you a sense of our thinking of not only the state of the science but how the state of the science interacts with the regulatory requirements that we're under.
The Food Quality Protection Act like David said requires us to do cumulative risk assessment of common mechanism groups, so we re under a mandate by Congress by August of 2006 to reassess all chemicals

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used on food and that part of that is doing the cumulative risk assessment for the N-methyl carbamates. 2006 isn't that far away on a regulatory scale right now.
We have now with the OP cumulative assessment gone through a series of more than 25 reviews of guidance, documents, methods, et cetera. if push came to shove today if we had to do a risk assessment we have methods that have been evaluated by you on the panel that have been reviewed by the public, if we had to today we could do a risk assessment using the models we have with approaches similar to the relative potency factor method. However with that said the Agency and OPP in particular is committed to improving our methods, improving methodologies and today's meeting is in evidence of that, but research and development of new methods is net order of process of development and review and refinement and development and review and refinement. It's unclear to us today the degree to which from a refined pharmacokinetic model will be used to quantify risk to this class of chemicals.

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However the models, the revisions to any of the exposure models, the development of the approaches, the experience we gain in the process will help us with future classes definitely, we also believe that all of this experience will help us at

minimum qualitatively characterize the risk to a class, so the degree to which these models are used to quantify risk and I mean with numbers is unclear, but at minimum it helps us with the future because we're committed to the new methods and for qualitative purposes, so with that said I'll keep going.

OPP's cumulative guidance document describes two broad kind of methods that you can use to do a multichemical/multipathway risk assessment. Broadly there's a relative potency factor or toxic equivalency factor-type methods that we use in the OP assessment and have been using other things like dioxin such as that. You could use effect levels like NOEL's or LOEL's but it's much better to use bench mark dose-type methods as we did with the OP assessments so things are on a common footing.

Broadly there is another set of methods or

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approaches you could use that are much more refined, pharmacokinetic models biologically based dose response models, so if we sound a little schizophrenic we're sort of purposely sounding a little schizophrenic. We have essentially two or three parallel efforts ongoing and you will see that in a few minutes. We're working on essentially two or three fronts simultaneously. As we have to have an assessment using methods that we can do to make the deadline we are working towards a relative potency factor based method, we're working with our colleagues at (inaudible) is working with us again to develop empirical based modeling of the dose response data for the cholinesterase data and then we're also looking at the recovery data to get a sense of the recovery of the compounds.

And just the essence of the RPF method is that you essentially convert -- the essence of the RPF method is that the potency of each chemical is compared against an index chemical so you have essentially units of chemical A, so chemical B is two times more potent, it's two units of chemical A

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essentially. And the idea is you need an endpoint where you have a common footing across all the chemicals so you want something with a common species and a common effect, so we're primarily looking at the acute studies in rats because we have rat studies for all the compounds and we're concentrating on the peak cholinesterase data and we're also looking at the recovery data.

On the PBPK front the fact of the matter is today there is insufficient pharmacokinetic data for all of the compounds to develop a multichemical/multicompartment PBPK model. You saw yesterday we talked about the PK data developed for carbaryl that is of all the 10 chemicals the best pharmacokinetic data set. We're very proud of our collaborative efforts ongoing with folks at the

Nuerolab in Las Vegas and also at Inhurl (ph) and CIT, we have a couple of efforts ongoing to develop a case study with multichemical PBPK model and over the next year you will see pieces of that.

The purpose of those efforts is to gain some experience as we see more data coming in to make those

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models more refined, and as time requires you have to develop tools and methods and we're going to get at that. So that gets us back to today, we need to develop some tools, not only is there insufficient data to develop a multichemical PBPK model, we also need to work out some of kinks of developing an actual risk assessment and part of that is linking PBPK models with exposure because the risk is both hazard and exposure. And that's mainly the topic of the LifeLine paper today.

So most of our current exposure models output distributions of exposure and what we need is information about individuals, not the distributions of actual measurements of exposure, we need the information on those individuals who are exposed. So that sort of brings us to today and what we're going to do over the next year or so today we're going to talk about the linkage between our exposure models, LifeLine specifically, and pharmacokinetic type models.

We will be back in February I hate to say another four days, but it should be a really I think

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exciting week, every day will be different, it will be a diverse set of issues and each building on because we're lead to the fourth day, the first day we're going to talk primarily about hazard assessment. We felt our great success with the OP cumulative assessment was our collaborations with scientists at Office Research and Development and we've continued those or actually expanded them actually, so on day one we'll have Stephanie Padilla and Ginger Moser and Woody Setzer (ph) all from the Inhurl Lab will be here talking about some experiments that Stephanie and Ginger have been doing and some empirical modeling that Woody's been up to, so we'll talk about cholinesterase inhibition a substantial amount on day one.

Day two we'll talk about some PBPK modeling on carbaryl and conceptual aspects of a multichemical model and primarily our colleagues at the Las Vegas Lab in Neural will be making those presentations. The third day our colleagues in the Environment Fate and Effects division will be presenting some ground model, exposure models. And the fourth day we're actually

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very excited about it, it is actually going to be extremely important to the overall development of our whole assessment and we're looking forward to the feedback that we're going to get.

The purpose of the day four is to present a case study which will essentially be in many ways what the assessment is going to look like, it will be a relative potency factor based assessment, one region, multiple routes, using food, water, residential exposure. And a lot of what we're going to want to talk about is both our current capacity and what we think are short-term future capabilities are going to be to evaluate recovery and how you would do that either qualitatively or quantitatively, so the feedback that we receive in February we think is very critical to us in terms of releasing the preliminary cumulative assessment which will go out in the spring, and that will be the assessment, it will be both hazard, food, drinking water, residential using RPF's for every member of the group, we will include eight regions in the US, we will be using three different exposure models, LifeLine, CARES, Calendex, (ph) and

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at that time it will probably qualitatively characterize cholinesterase recovery on the risk estimates.

We will be working towards a winter 2006 revised assessment which all leads into the August 2006 FQPA deadline for (inaudible) assessment. So you have today what is a series of meetings and we're continuing to follow a very stepwise methodical, transparent approach to developing our methods and our assessment. We believe that there are some revisions that are needed to current exposure models to make PBPK models another pharmacokinetic type modelings more operational for developing our assessments, so that brings us to the purpose of today, we're looking forward to some comments on both conceptual and technical aspects of LifeLine's proposed revisions.

DR. HEERINGA: Thank you, Dr. Lowit and Mr. Miller for your presentations and I think at this time we're ready to move onto the next topic on the agenda which was the presentation by the LifeLine Group, Dr. Chris Chaisson and Ms. Clair Franklin and Mr. Paul Price.

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DR. FRANKLIN: Thank you, Dr. Heeringa. I am very pleased to be here this morning along with my colleagues Dr. Chris Chaisson and Mr. Paul Price. Together we will be making the presentation which highlights the key points that are discussed in more detail in the document that has been made available to you, and I point out that it's also available on the EPA site.

As said already by Mr. Miller we're very enthused and very keen to have your feedback and comments on the document and what we're proposing to do. I think it will be very important that at this early stage we have as much scientific input and advice on how we move forward with this. I point out that the LifeLine Group is a not-for-profit

organization of 501 C3 with a mission to develop technically excellent tools for characterizing exposures to chemicals in diets, residences, consumer products, and occupational exposures and resulting risk. The intent of the company is also to make these tools available to all interested parties, it's distributed free, and I think it's important to point

out that the LifeLine Group is committed to developing open tools, no trade secret model components, and all working elements described in open technical documentations, so there are no black box approaches, I think this will be particularly important as we move forward with an exposure model that will then feed into a PBPK model.

The objective for our presentation today and I think for the EPA objective is really shown in the fact that we need both a robust exposure model, very critical to have a robust model as well as a robust PBPK/PD model. I would like to emphasize the presentation today is not about the PBPK/PD model, it is focusing on the exposure model that will deliver to the PBPK/PD model information about people, their exposure profiles by route, their relevant physiological parameters related to estimating tissue and cellular dose. Its it's important that we keep that in mind as we go through the discussion today.

I would also like to emphasize that the concepts presented in the paper are generic concepts, they're relevant to the scientific task at hand, does

not issue specific to LifeLine software only. We're certain that LifeLine software can be amended to accommodate these concepts and the resulting approach will be capable of assessing a true cumulative exposure profile and that it will also fully compliment a PBPK/PD model for carbamates or for that matter as we've indicated in the paper it's important that it would be able to be used for other chemical classes as well.

The approach concepts and opinions described here and in our paper were presented to EPA ORD who were involved in developing the PBPK model. We certainly did not want to come forward with a proposed model that wouldn't meet the needs of the recipient model that would have to have this information, so that we have entered into numerous discussions and feel very comfortable that the proposals that are in the document that you have will meet the needs for their model and as we've indicated in our document for other PBPK models that will come forward in the future.

The issues that we want to highlight and

because of the time we really are not going to go into enormous detail on all of the issues, you have the paper and I know you will have looked at that and have

questions, but the issues that we would like to highlight are nomenclature, we have of course issues with terminology, exposure versus dose residue and exposure et cetera. To emphasize the existing exposure assessment embodies the following, that the time unit is a day or longer, that the data base really is a true aggregate data base, there are multiple simultaneous sources that can be aggregated and presented as source-specific or route-specific exposure. Cumulative is not really cumulative yet as already been mentioned this morning and that it's done on a chemical-by-chemical use of residue data, that there is no linkage with regards to probability of occurrence and magnitude of residue if occurrence is likely.

The next challenge of course that's before us today really is the carbamate issue, and in order to move forward on that we need to have a true cumulative assessment. We need to be able to link the

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physiological parameters and demographics morphometrics to get to the absorbed dose. There's definitely a need for shorter time steps, we certainly heard yesterday that carbamates, carbaryl and particular have very short half-lives so that it will be very critical to have shorter time steps, and we also have to have residue data for multiple chemicals linked in terms of magnitude and probability of occurrence.

The issue with regards to terminology and nomenclature I've captured on this slide. I would like to point out that there's been a very large inactive international activity through IPCS, the International Program on Chemical Safety, which is a WHO activity, to try to standardize terminology in this field of exposure and absorption because there are a myriad of terms that are used and they're not necessarily always utilized in the same way.

The purpose of putting this here for you today is to at least give you and there is also a glossary in the document so that we're all on the same page when we're talking about these various terms

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because I know they are utilized in different ways. Exposure really embodies ambient levels and that can be simply measurements of the concentration in air, can be food residues, concentration in water or on surfaces which is of course important for residential exposure.

The next compartment, if I can use that term, is really the contact exposure, it's sometimes called the contact dose, and this is really the amount of the chemical that impinges on an absorption surface, this is the skin, the alveoli, or the gut. Now it's very clear that they're not inside the body when they're at that point, but from a physiological basis it's also of use to know what the intake is and from that one

could certainly get an estimate of the amount that would be at the alveoli surface and at the gut surface.

The next step that happens in this process is that the material is absorbed and it can be absorbed and the measurements can be looked at, the levels can be looked at in blood, in tissue, or actually right at the cellular level. Another term that's used there is

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uptake and some people use that in essence as an analogous term to absorption, that's usually expressed in either terms of percent absorption or flux.

This is really just to remind us where we're at with the cumulative assessment and to point out that this is really -- the one that has been done has been based on relative potency factor and as you can see in this diagram on the left-hand side there are a number of chemicals that can be taken into consideration, they can have varying amounts of data in the data base, but the RFP is really -- excuse me -- the RPF is really selected on the basis of the common toxic endpoint. And the residue data are then converted from the multiple chemicals into a data set so that in fact it looks like one chemical, the model thinks it's seeing one chemical, the reference chemical, all models do this, we're not aware of anyone who is doing a truly cumulative exposure assessment. And the downside of that is that the individual chemicals lose their chemical specific identity in terms of some of the parameters.

We now turn to what we feel is really quite

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essential in that that is how do we do a true cumulative exposure assessment and how do we interface with the PBPK model. In real cumulative model there is no reference chemical, there's no toxicology equivalence and the chemicals are entered directly into the model with all of their own data, this can be down and this will be described by Chris and Paul.

The advantages are that the toxicological and biological parameter stay linked to each other and that information can be passed onto to the PBPK/PD. As you can see in the column with the darker orange the model can in fact provide the information as an ambient concentration, it can provide it as a contact exposure, and it could provide it as an absorbed dose, that's really the interface area and it is then very important that this, whichever of these methods or types of data are then able to be transferred into the PBPK model, the advantage of having the exposure model set up that it can deliver the data in those three types of packages is that it would then be able to interface with a wide range of PBPK models.

And with that I'm going to turn the floor

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over to Dr. Christine Chaisson.

DR. CHAISSON: We're optimistic that the

science and the technology exists to develop a PBPK/PD model and assess risk at this refined level. We're confident that we can make a positive contribution toward that goal and have presented our ideas for your consideration. We think there are at least three critical issues that deserve some careful deliberation and before Paul Price discusses the overall approaches we wish to highlight these for your consideration.

We recognize there's no perfect way to create a model like this, but we need to make sure that it's done right and that these kinds of points are given their fair share of conversation if you will. So with that we would like to start with the timesteps. As Dr. Franklin said one day is just not good enough, presently the smallest increment of time for which the exposure metrics are calculated is one day, the PK/PD model will be considering units of exposure at the cellular level that will inhibit cholinesterase, within a reasonably short period of time that inhibition will cease, the exposure metrics must be

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described for time intervals relevant to this enzymatic process, this the resolution of one-day exposure metrics is not adequate, the metrics should be in terms of minutes if at all possible, this creates the need to order the exposure scenarios throughout an individual's day.

We must revisit the way in which exposure opportunities have been described for individuals. Previously we could just sort of pile up all of the exposure opportunities of a day, several meals, some snacks, playing with the dog, cleaning, et cetera, that yielded a per day exposure assessment. Now we must order those activities so we know what happened within small intervals of time across the day. The elements to be considered in this process includes obviously what are the daily activities, but then also durations of those activities and ordering in a logical way some activities also that are mutually exclusive so we can't have dinner while sleeping, so where will we get this information and what is the smallest time step that we can construct from that information.

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Again as usual it's highly unlikely that any one data base will deliver all the information we need, and again we will need to walk across data bases to harvest the information in a coherent and legitimate way. To do this we return to our transition principles which we presented to the SAP on several occasions previously, those are rules that detail the order of association between common elements of different studies to link information that describes people starting with permanent features and then proceeding through periodic or transient elements.

So what do we need to know. Well, what we

do, we need to know at given parts of the day are strongly correlated to factor such as age and gender, regionality, urban and rural living, and socio-economic status and season. These correlations help to link the information about people from one data base to another and they become the bridges the link the data with those linking rules that we call transition principles.

The task of ordering individual activities

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across the day will likely employ multiple data bases because both breath and depth are required for this task. The descriptions of activity must satisfy the EPA need to address the full range of our population subgroups within the United States, in all regions for all seasons, in all ages, both genders, all ethnic and socio-economic groups. But at the same time for the individual we need to know the what, when, how long, et cetera, for each activity or be able to drive it from multiple information sources, that is doable and we can construct a coherent and representative ordered daily activity pattern creating what we call an event framework.

The keystone to this task as we see it is the United States Department of Agriculture's continuing survey of food intake by individuals, shortcut CFSII. We have used the information in this survey for telling us how much of what food was eaten by each respondent per day, and you're all familiar with that.

The survey however contains much more information which sets up a beginning for the linking together the activity information. In the future

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NHANES studies will also fill this role. The linkage will again follow the rules and principles, it cannot be an unstructured intuitive approach to putting this kind of thing together.

In the brief amount of time that we have here I just wanted to present a few quick glimpses of the kinds of data within CFSII that helps us to do this, the first one is about time. The study actually tells us when did the eating event begin. Even if you have breakfast at 3 a.m. or 4 p.m. it is recorded and we can capture to set up eating occasions as the first of the activities within the framework.

Another thing that's in those records, each eating event has a name, for example breakfast. This description made by the eater reveals what they considered the event to be and conventional ways of thinking about it. We can infer from these descriptions something about the event including how much time was spent on that eating occasion.

The smallest unit of time we can infer from these descriptions is about 10-minute periods for something like a food and/or beverage break. If

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that's a 10-minute event then we can assign lunch to

be considered a 20-minute event on average or a two-time step event. These are somewhat subjective but they're reasonable and they're grounded in the actual data within the CSFII.

Also the CSFII records tell us about the meal preparations, where the food was prepared, where was it eaten which is frequently a different place than where it was prepared, and permits us to refine the framework to know where the eating event occurred, was the person at home. As a model is constructed a detailed description will be presented on how these activities were ordered, suffice to say this growing library of information of activities and CFSII provides a reasonable foundation for ordering activity files in a coherent, reasonable, and representative fashion. It's not perfect as the ultimate activity exposure survey would be, but we can model the scenarios from the abundance of information and the framework that CSFII provides for this at this time.

This illustrates the results of this approach. Within every hour of the day you order the

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activities into 10-minute timesteps using information about the activities that are coherent for that individual, their gender, age, economics, living conditions, season, et cetera, so we are not just taking all of the day's exposure and apportioning it evenly to every timestep, we are making exposures -- the exposures are not arbitrarily apportioned, rather the activity patterns are ordered in a coherent activity pattern for an individual's characteristics starting with the CSFII. Consequently, these exposure peaks will fall where they may and the absence of exposure opportunities will fall where they may.

The second issue is about the residue data relevant to cumulative exposure assessment. This is an illustration of an entry from the pesticide data program monitoring crops for co-occurring pesticide residues. In this example there are six pesticides assayed on a single carrot sample, it's unlikely that the use of these pesticides on those carrots were random, rather they were prescribed application principle dealing with given pest pressures, therefore the probability of occurrence of any one chemical is

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related to the occurrence of the others. Likewise it's possible that the magnitude of the residue of any one chemical is related to the magnitude of the residues of the others.

What then if we assume there's no major change in either the pest pressure or the pest control strategies and we are considering regulatory options that could add a new chemical within the class of chemicals perhaps a competitor, one that's already been on the market or we wish to delete the use on carrots for a pesticide which was one of those six chemicals measured in the monitoring study, how would

that affect the probability of occurrence of the other chemicals and the magnitude of their residues.

Illustrate this, let's say we take out pesticide A and B and we want to know then prospectively what would the probability of occurrence be for C, D, E and F and what would the magnitude of those residues be. There are a series of these kinds of considerations to be made.

The question then is how to model the new residue occurrence profile, that will be discussed in

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a separate paper that we're presently writing for OPP. We mention it here because it is a key component of the cumulative exposure issue and directly relevant to the cumulative assessment of the carbamates, and of course subsequent consideration of regulatory options for that chemical or for other chemicals in the future.

The third issue is the interface design issues. We have to think about this very carefully because we're delivering data from one model into another. There's going to be a very large volume of data being delivered to the PBPK/PD model. We have to make sure that there's a good linkage of the physiology and the demographics and exposure calculations. This interface between these two models need to be seamless, there can be neither gaps nor overlaps. I will explain more about that later.

They also have to have flexibility to tailor the output of the needs of any PBPK model and the user of the exposure assessment model should have some flexibility to decide what they would like to carry over to their PBPK model.

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To illustrate the situation at hand the exposure assessment models can accomplish tens of thousands of relatively simple mathematical calculations in very little time and can store large volumes of answers in attendant tagged information in its output. The PBPK/PD models utilize pharmo complex algorithms and with more time consuming mathematics. Because of is inescapable fact the PK/PD models will run a little bit slower.

This is a typical output for LifeLine, it's a large data file and with the 10-minute timestep it would include 10-minute timesteps for 24 hours per day for 265 days a year for 85 years for about 10,000 people, that's a lot of numbers. For each exposure in addition there would be an exposure record by route, one by source, and one totaled, accompanied by the individual's physiological, demographic, anthropomorphic information for each life period of growth and maturity. That's a very large volume of data available to be transported to the PBPK/PD model. Of course if desired all of the information could be transferred, but if that large volume is not desired

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one could filter the information delivering only a fraction of the data, actually all the linked data for a person, so we're really saying that the individuals must be filtered.

So which individual to filter out, which one should be transferred. There are many options for defining this filter and the user must understand what is being taken out and what's in effect being sent across. Here are three options although obviously there are many more, because EPA traditionally regulates in consideration of the top percentiles of curve those individuals at the top of this distribution curve obviously could be one group that an assessor might like to have transferred over to the PBPK model.

However there are other regions that could be chosen for their use, you could take every say 50th person, every 250th person all the way from one end of the distribution to the other, transfer that or maybe you're just interested in the mean or median or some statistically defined part of that curve for different reasons, for research or for different reasons for

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regulatory decision making the user should be able to decide where and what individuals, where to focus and what individuals to transfer.

The interface must provide flexibility for the user to select those physiological parameters of interest and transfer only those. Even though we can provide information on all of these points, if you're only interested in the liver then perhaps there's no a need for you to be inundated with all of the tagged information on the rest.

The user should be able to define which metrics to transfer and which areas of exposure distribution curve as I just said, these were some of the issues that Claire talked about a little earlier.

The user can decide whether to use the exposure or dose or ambient level and the metrics including or not including absorption, it's very important that the user know whether or not the exposure model has already considered absorption because you don't want to either double-count it or fail to count it at all which is illustrated on this next slide.

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There are many efficiencies for meshing two models rather than creating just one huge giant model. Both models can evolve independently and approve without requiring recompilation of the entire universe. Care must be taken however in the maintenance of the interface. Information can be delivered from the exposure model to any PBPK/PD model. Once again we have to be sure that the people understand the algorithms that are in being selected now the exposure models so they neither double-count say in this case you would have double-counted the

metrics or the algorithms for calculating absorption twice. And in this situation neither model considered absorption so we have to be sure that the users understand what they're selecting.

Thank you and I think now Paul will show you how we plan to put all of this together.

DR. HEERINGA: As you can tell from the shape of the slide I am going to talk about flow charts and therefore it's long and narrow, so I will give you that warning and you have copies of the flow charts which might be a little bit easier to see than on the

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screen. Chris and Claire have set up the issues and Chris has talked about some of the key new concepts that have to be incorporated into exposure modeling for the first time in order to do this.

I am going to talk about the overall structure or the architecture of the model, how that needs to be changed in order to achieve this and how that structure needs to be set up so we can incorporate the pieces that Chris talked about.

LifeLine is a person oriented modeling and this is a category of or a fundamental design for exposure modeling that places the person at the center of the model rather than the source of exposure or the mechanism by which it moves to the environment, so it really says that the person is king. And by beginning -- and this is not restricted to LifeLine, this is a characteristic that applies to most of the exposure models that are currently being used to investigate pesticides.

Once you've defined a person or you begin the model by defining the person assigning them fixed characteristics or characteristics that change in a

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known way, are they male, are they female, where do they live, what's their ethnic background, what's their income level. And based upon those characteristics you then can define in a way that's consistent with those definitions what's the type of diet they have, what is the type of home they live in, what's the residential use of pesticides, what's the behavior of the individual that's relevant for determining how they interact with those pesticides in their homes. And this focus on the individual we believe provides an excellent foundation for the design of exposure models that will support PBPK/PD analyses.

This is going to bounce back and forth a couple of times to talk about the points and where they show up in the LifeLine software design. I'm taking some time to talk about the LifeLine software as it currently exists, I'm doing that because not everyone on the SAP has had the chance to hear our presentations on the fundamental design of LifeLine.

We start off by defining the individual and as I said assigning him fixed characteristics or

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characteristics that occur at the beginning of the person's life. We then after we have defined the person we go into what we call our event loops, now this is a structure inside the computer program that cycles through and performs the same task multiple times, and each time you begin an event loop you start by pulling a record which tells you how many times you'll go through the loop and what you'll do in each one, in each cycle of it.

So the first type of event we would like to talk about are the ones that we use to evaluate diet and they begin by pulling a daily record from the CSFII and then they loop through each one of the foods that are consumed.

And here you can just barely make out the looping structure that begins by saying first pull the CFSII record and then first thing you ask the question is in the first food was there a residue you cared about, if there was you calculate the dose that came from consuming that food. If there was no residue you skip that and you go onto the next food and you repeat this cycling through each food that was consumed in a

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given day tracking the doses, adding them up until at the end of the day you have the dose from the diet.

We did the same approach for our non-dietary exposures, instead of pulling a record from the CFSII we pull a record from an activity pattern data base and now instead of looping through foods we will loop through microenvironments.

So now you have a second set of loops that again begins by pulling an activity pattern record and saying in the first microenvironment which might typically be bedroom and say sleep from midnight to sometime in the morning and say is there a residue that occurred in that microenvironment and did you receive an exposure. Now for this portion it's very important that we determine not only the dose that happens from oral exposure but also by inhalation and dermal. So at this portion we're tracking dose specific -- I'm sorry -- route specific doses.

Once we have gone through the dietary and the non dietary we've completed the exposure that happened on the day and we repeat the process for the next day. And as we repeat the process we change the

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environment, maybe the season has changed, maybe they have moved from one house to another, but whether there's been a change or not they're certainly going to be eating a different diet and they're certainly going to have a different activity pattern, and as a result will change the records that are pulled for the subsequent days.

This process cycles through, first cycling through the event loops for the diet and the non diet and then cycling through the days until we have

finally described the exposure history of the person. That's what we do right now. So here's how we're going to change that structure to meet the needs of PBPK analyses. First off, we're going to change the time structures. Instead of cycling through it on days we're going to cycle through on a much shorter period of time, and we're very fortunate that the LifeLine structure is amenable to this, the looping structure doesn't care if it's cycling through a day or 10 minutes, it's simply the design that says at what point do I start looking at different types of data.

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And because of this flexibility you don't have to change much in the model, and it also means that in the future if you want to do a model where the timestep is one hour or ten hours it's a very easy matter to have the user be able to specify it at the beginning how long they want the timestep to be and to literally solve for it on the fly.

The second area we need to talk about is how we're going to go from our current structure which only models one pesticide at a time to modeling multiple pesticides and how the model design will facilitate the determination and the separate tracking of those. And finally the last area we will talk about how the focus of the individual will set us up so we can move on from talking about body weight to talking about things like blood flows, compartment volumes, and how those change with activities.

Time change, as Dr. Chaisson discussed and as we all heard yesterday, it's critical to move from time periods of one day to shorter time periods to be able to support PBPK modeling because the time scale of the events is so much shorter than one day. In

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developing this there's two terms I want to talk about, one is this idea of the brief timestep and the second is the concept of linking timesteps together to create an exposure history, and the last point I want to talk about is data issues.

The way to support a PBPK model is to model an individual up to a certain point in their lives and then at that point define what their characteristics are, their height, their weight, their physiology, where they live, type of house, region of the country, season of the year, et cetera. And then go into this excruciating detail of modeling 10-minute intervals over a period of time. And the kind of framework we're working on is we will do 10-minute intervals and we will do it up for 24 hours so as a result we're going to have 144 10-minute timesteps. And then for each of these timesteps you would define what was the exposure that happened during that timestep and what were the does that occurred as a result of those exposures.

Now the design of the model doesn't care how

long the period of time is, but what it does care is
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at the beginning it needs a record to pull from, but where we have one day we pull a CFSII record or activity pattern record, now we need a record to pull from that describes just what happens in that 10 minute period of time, and that process is what Chris outlined is that we need to have a technique that goes through and says given an existing set of activity patterns how do we develop a combined dietary and activity pattern record that describes what happens in a 10 minute period of time. And we believe that an approach like that is feasible and the way it will fit into the model is shown in the next slide.

Here we have again as LifeLine begins we start off by defining the individual's characteristic. The first step the model will do is to say given who you are and given where you live and the season we're going to pull the appropriate activity pattern and the appropriate dietary record in and any other information that is relevant to defining your activity patterns and then we'll invoke this module which will say given two inputted files create now the 144 records that will describe the activities that
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happened on each of these 10-minute timesteps.

Now once this set of 144 records is created, now we can simply use those to cycle through and to ask what is the dietary exposure that happened during that period of time, what microenvironment are you in during that 10 minute period of time and what are your doses that happen as a result of interacting with pesticides.

And we'll cycle through each one of these 10-minute timesteps until we have completed the exposure history for the individual. Now when we are done we have a 10 minute description of the doses that happened by individual routes from dietary and non dietary exposure to the individual nicely separated out ready to be shipped over to a PBPK model to be used as inputs.

The next area I wanted to talk about is how we are going to model multiple pesticides, and the challenge of modeling multiple pesticides rather than one really falls into three areas. Chris has talked already about the challenges of how we need to change how we organize data on residues, it's now critical
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that we track the residues as they occur on a food item so that we capture the correlation between the different pesticide residue levels.

Once we have done that and we have our data organized in the appropriate fashion we now need to change the model structure so that we separately track each one of the pesticides and we will do that by creating a new side of nested loops, and finally we need to talk about how their going to generate

outputs.
This is the worst of the slides and I'm very unhappy to see that you can't see the color changes so you can't see the differences between them. Let me see if I can do something with the laser.
Basically up here has no change from the slide I showed before, we start by defining the person, pulling the records and create our 144 timestep activity patterns, but then when we get into the first activity pattern we say during this 10 minute period of time what did you eat and if you ate a particular item it says okay which were the residues that were on that food item, and then you would say

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was the first pesticide in that food item, if the answer is no you got no dose from that pesticide, if the second pesticide was in there yes it is there, you did eat it, you got a does, so we will now say for each food item what were the doses you received from each of the end pesticides that are in the common assessment group. And we will separate -- we will keep these doses separate, we will store them in a matrix these says for a timestep of consuming food these are the doses from each one of the -- these are the doses of each one of the pesticides that happened during that 10 minute period of time.
Because we keep them separate we will always be able to go back and be able to talk about the time course exposure for each pesticide on a 10 minute time period of -- on a 10 minute timestep over the entire exposure history. Once we have gone through the first food we have to go through the next food and we repeat the process of looping through each one of the pesticides again for the second food, and we will repeat that for every food that's consumed during the 10 minute period of time.

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Once we've done the foods that were consumed during that 10 minute period of time but then go to the microenvironment the person is in during that 10 minute period of time and say is the first pesticide present in this microenvironment. If it is we calculate the dose, if it isn't we go to the next pesticide. So by creating this intersect of loops where we cycle through each pesticide, we evaluate each food and each microenvironment we generate pesticide specific estimates of doses that characterize the mixture or sweet of pesticides that the person is exposed to for each one of these timesteps and then we save that as an amended or an expanded exposure history for the individual and have that available for the PBPK model.
The outputs, the outputs are going to be as we've proposed in an access data base that will have structure, in the structure it will say, it will define the individual's characteristics and then for each one of the timesteps it will specify for each one

of the pesticides of interest, the dose that was received from that pesticide, the source of that dose,

and the route by which the dose occurred.

The structure that LifeLine has used in the past for organizing data and tracking data has the ability to be extended to handle this additional level of complexity and to organize the outputs of this in a format that will be appropriate for PBPK/PD models.

The last area I want to talk about is extending the definition of the person and the advantages that that provides to PBPK/PD modeling. I am going to talk quite a bit about the P3M project which was a project that the LifeLine staff were involved in to develop an approach for modeling the physiology of individuals in a way as a means of supporting PBPK models of variation in pharmacokinetics.

Secondly, I want to talk about how we are gong to incorporate that into LifeLine, and then finally talk about how defining the person might give us an edge for talking about some other issues which are relevant to modeling individual variability.

The P3M project was funded by the American Chemistry Council as part of its long-range research

program and we received funding to develop an approach to -- to provide the physiology data that PBPK models require for modeling interindividual variability. These types of models require information on how tissue volumes, blood flows vary from one individual to another so but also how the values in an individual are correlated, so you don't have a huge body weight, small liver size and inappropriate blood flow. And the project resulted in the production of a piece of software called P3M which is publicly available through the LifeLine web page.

The parameters that were investigated in this project included the values of a large number of organs and tissues, the blood flows for these organs and tissues, and the total cardiac output under resting conditions and the average daily inhalation rates. And the values were calculated for roughly 30,000 individuals who were evaluated in the entry surveys and was published in the peer reviewed literature and there's the reference.

The project is intended to be evergreen. While we received our initial funding we've received

funding from some other individuals to maintain and to improve the software, version 1.1 has already been released and version 1.2 is currently under development.

And it is easier to see in your handout, this is a copy of the interface for it and you basically can go in and select those parameters that you're interested in, you don't have to take every possible

parameter in order to use the model.
The approach that we used is to go to the literature and identify equations that related height and weight and age and gender to the volumes of various compartments. And we applied those equations to data from the NHANES data set and when we got done we asked the question well our volumes, did we really capture the correlation, and we came up with a simple way of dong a test for it and the test was if we took all the estimates of the tissue volumes for an individual, divided them by the densities which would give you then the weight of each of those compartments, the tissues corresponding those compartments, some of those weights and then divide it

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by the person's reported body weight, and if the answer is one then our estimates of volumes correspond to masses that add up to the reported body weight and we probably did a fairly good job.
And the chart here shows you the 30,000 individuals at NHANES plotted the ratio of the predicted weight divided by the body weight as a function of age, and what you can see is that the models we found that worked for adults, individuals over age 20, really seemed to do a very nice job of predicting volumes that corresponded nicely to body weight.
For individuals under the age of 20 because they grow they're regression equations, actually had some real difficulties in trying to accurately predict some of the compartments and we wound up being off by about 10 percent for some of the age groups, but again even there the impact is fairly minimal. So we took away from this test that P3M is doing is a good job of accurately capturing the interindividual correlations between the compartments.
The way P3M works is that it draws upon the

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anthropometry from the NHANES three records, age, gender, ethnicity, hematocrit, height, and weight are the parameters that they pull in. LifeLine already determines the anthropometry with the exception of hematocrit for each individual model, for each year of the individual's life. Because of this the same equations and approaches there were used in P3M can be directly extended into the LifeLine software and as a result for each individual we create in LifeLine we will be able to do the same thing that we did in P3M and create estimates of their physiology that are relevant to PBPK modeling.
There are some physiological parameters that are constant over a one day period of time and you can simply see a value at the beginning of it and the same die could be used at each timestep. There are others that are others whether this is not true where they change as a function of the individual's activities and the individual's diets. And these three things

that change or the things that do not change are things like compartment volumes, you're liver's the same at the beginning of the day then at the end of the day, one hopes.

But your breathing rate and your cardiac output will vary from minute-to-minute as a function of what activities you're involved in, and the fraction of where the blood flows into which compartment will also vary as a function of your activities and also what you have recently consumed. And because of that we need to have the ability to define the physiology and how it changes as a function of the activities of the individual and LifeLine framework will allow us to do that.

We already are calculating activity specific breathing rates which we can then take to the alveoli ventilation rates very easily and there are approaches -- since cardiac output is closely tied to breathing rate there are ways of predicting how the total cardiac output will change from as you go from a resting activity to a more active activity.

And then there are also equations out there that indicate how changes in the fraction of blood that go to the different compartments might also vary with activity and diets, so after a meal the amount of blood flow going to the GI organs will increase. All these things can be capture inside the of the LifeLine framework.

The process for capturing it is given in this flow chart where we use the fixed characteristics to define the age, gender, and ethnicity of the person to define their height, weight, and surface area, then we use the equations from the P3M process to come up with the compartment volumes and the resting cardiac output and alvelolar ventilation rate and then we take the information on diet and activities from the timestep records to combine together to come up with the predictions of the timesteps specific cardiac output ventilation rates and compartment specific fractions of cardiac output.

The result is we will be able to supply tables like this as part of our exposure modeling to the PBPK analysis. The top table shows the fixed values of physiology that do not change and they're divided into demographics and the volumes of the selected compartments. The lower table which only three lines are shown and actually there will be 144 rows in the table shows the alveloar ventilation rate, the total cardiac output and the fraction of cardiac output to each of the compartments for each of the timesteps over the 24 hour exposure history.

We think that framework will be an effective way to provide the physiology information required by the models, but we can actually go beyond that.

Because we've defined the person, who they are, how old they are, what is their ethnicity, what is their race, what is their gender, that information can also be used to provide the basis for putting in information where it's available on genetic variability. That if you have information enabling to link to those factors because you're the framework you will be able to capture that information inside of these models.

In addition to genetic factors lifestyle factors, is the person pregnant, are they a smoker, do they suffer from a chronic disease, can be captured and incorporated as well because the demographics of those factors are available and can be linked back to the demographics of the person that we've defined in

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the model. And finally, data on the frequency of transient effects such as colds or other illnesses can be incorporated into this frame work.

In summary we believe that the framework under which LifeLine and other person oriented models were created together with the work on P3M allows for all of the modifications necessary to provide the exposure and physiology data that are required by PBPK/PD models, it allows you to change the timesteps in a very flexible fashion, the approach of deriving these 144 separate timesteps from the larger data sets I think is a potential to be a very flexible and useful approach, the framework is readily extendable to going from one chemical to multiple chemicals and tracking multiple chemicals so that we have the ability to deliver a truly cumulative estimate of exposure, and the person specific focus provides the foundation for providing the physiology and other factors necessary to define interindividual variability in the PBPK/PD models.

Second, the technical issues at which there are a number of them and we are looking for your help

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today we think are solvable, that there are manageable and open and transparent ways of achieving the goals for all the technical tasks necessary to support PBPK modeling.

And finally, we want to stand up and salute to say that whatever exposure model is used there has to be a very careful dialogue between the exposure, modelers, and the PBPK modelers to make sure that the interface is truly seamless, we find that language and tradition often make it difficult to communicate from one group to another. Thank you.

DR. HEERINGA: Thank you very much Ms. Franklin and Mr. Price and also to Dr. Chaisson and to the staff of the EPA for some very concise I think and informative presentations, you have done well for putting us on a good schedule for today.

What I would like to do we want to have a period of questions and clarification but I think we

all require a break but before we do that I would like to one more introduction Dr. David MacIntosh has arrived to join the panel this morning.

David, if you would be willing to give a little bit of your background.

DR. MACINTOSH: My name is David MacIntosh and I'm currently a senior scientist at a private firm called Environmental Health and Engineering in Newton, Massachusetts. I have a background in exposure modeling with aggregate and cumulative for pesticides as well as heavy metals and microbiological agents.

DR. HEERINGA: Thank you very much, Dr. MacIntosh. At this point in time I am going to call for a 15 minute break, if we could be back here at 10:15 to resume and at that point in time we will have our general comments.

I would like to try something on the general comments or questions since I am sure everybody has them, rather than going in sort of a random walk order I think I may go systematically around the table once and then come back to individuals who have additional questions of clarifications, if that works for the panel I think I will give that a try just to make sure that everybody has a chance in some order to ask their questions.

(Break.)

DR. HEERINGA: Welcome back to the second part of our morning session of the FIFRA SAP meeting on the topic of the N-methyl carbamate cumulative risk assessment. We have completed our presentations by the research staff of the health effects division and also by the representatives from the LifeLine Group and we're about to enter a period of sort of questions and clarifications on the part of the panel.

Over the break I did a little bit of contemplation and I think instead of going systematically around the room I want to make sure that everybody has a chance to ask their question, but I think the way I would like the organize it is I would like to begin with the lead discussants of each of the questions and for question number 1 the lead discussant is Dr. MacIntosh. Dr. MacIntosh did you have any points of clarifications that you would like to raise or questions?

DR. MACINTOSH: Thank you for a opportunity. I can ask a couple of questions that I've had in mind. And I have this in my notes already so I won't ask it again.

So it's interesting to me the idea of going from the one day time unit for LifeLine in related models to a much finer time resolution in the 10 minute, and the use of the term timestep throughout the report that we reviewed for question 1 also intrigues me in this sense, and when I see timestep I

usually think of a dynamic model, time dependant model, one that is composed of one or more differential equations that are if more than one in the system yet I see no mention of that in the report, and so my question is is the concept to produce a time dependent dynamic model or is it to produce a steady state model that's based on linked consecutive 10 minute intervals or is it something in between?

MR. PRICE: It is the former, it is not a differential equation based approach, it is essentially built onto the idea that you should try to get as fine a time scale as you can as is necessary for the time scale phenomena you are trying to model. The rule of thumb is you would like to get it down to the point of where you can -- all your parameters assigned for that time step can be handled by single

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values or can be handled by some type -- or can be averaged to single values.

And your limitation, there's always the two-fold limitations, the finer the time scale the more row sources is required that's not so much trying to find data that makes sense on that time scale, and the data that we have to enter into variability a large number of people is macro data. We have some information that's fine enough like the start times for meals, the start times for blocks of events, but we simply don't have the data to allow us to go down to that fine level, but the model is fundamentally a set of discreet of models, the discreet event models.

DR. HEERINGA: What we will do is we will have clarifications on those issues.

DR. RYAN: I have something that falls directly from David's question and Paul's response to it. Have you considered any type of -- once again using the differential equation type of framework, some type of adaptive procedure whereby the size of the timestep would be appropriate for the change in the exposure that might be, that could certainly save

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a lot of computational time for instance while an individual is sleeping they're taking in you know a whole bunch of things, they're not eating, they're not doing a lot of things, they're breathing might all be the same, and putting together some kind of program where you say okay for the next eight hours it all looks like this would be a lot easier than doing whatever that comes out to be 80 different timesteps for the solution.

DR. CHAISSON: There are going to be several layers of conversation when we get to how do you link these and I was obviously emphasizing this need to go cross data basis as Paul said there is no at least -- if you know of any 10 minute exposure assessment surveys please let us know, but I don't think that such a thing really exists per se for certainly a broad spectrum of activities.

So there are several of conversation and we're going to have to go across it. Now one of the things though that we try real hard to do is that when we build a new structure that we preserve the ability for the structure to be expanded later on, so we don't

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want to build something that's linked for eight hours in static when tomorrow we may might need that period of time for whatever reason to be further broken in so we tend to air on the side of making things system wide and assuming that even though nothing's happening that we know about right now for those eight hours maybe next time around that those eight hours will become a focus for some other reason, so just without dealing with any specifics.

Now on the other hand if we run into computational time problems obviously we're going to have to find some shortcuts, but I'm less concerned about that with today's technology than I am just of getting it right.

DR. BRIMIJOIN: So I'm a naive outsider here who is obviously been asked to read this to see if this is comprehensible to maybe a more general toxicological audience. My question is I'm trying to figure out what this model is really doing and I come to the understanding that it's first of all trying to decide okay what kind of a person do we have here right now and what are the person's characteristics

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and then going from the characteristics it reaches out to data base of records that will provide information about activity patterns, eating patterns, selection of foods, and then in turn we can go to other data bases and other records to know what kind of that residues might can be encountered and that's the essence of it, so that's generally correct.

More specifically I'm wondering if -- and we're doing this on a daily basis and we're not trying to carry things over from day-to-day, so because not necessarily in the case of these short acting compounds we expect their effects to be gone so each day is a new day and we're going to calculate a new bunch of exposures, that's the background of my question.

My specific question is once you have decided for this day that this person's characteristics for that day or even that time of that day based on their varying levels of activity are we going to a rather fixed set of records saying if it's this kind of person he's going to eat this thing every day at this time or are we going to go and maybe in each timestep

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select from a universe of probabilities he's in this category so he has this probability of eating now and of eating this thing and therefore encountering this residue, so is it more a stochastic sort of approach?

MR. PRICE: It is a more stochastic approach.

I didn't go into the details but there's a whole philosophy behind LifeLine that says that you decide up front even before you deal with the person you decide who your population is and from your population you select individuals that are statistically representative of the population and you would select many of them so you capture the variability across your population.

DR. BRIMIJOIN: That was clear but I wonder once you've gotten your individual whether he was behaving like a clockwork robot or again whether his activities would be variable, his or hers from day-to-day.

MR. PRICE: If the next day is a weekend they will obviously have a different activity pattern, they eat different foods on subsequent days so each day is different. Now we only talked about one day because

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the carbamate kind of framework lends itself to that, but if we had a chemical where you worried over a seven day period of time each day they would have a different diet and each day they would have an activity that would reflect is it a weekday or a weekend day.

DR. BRIMIJOIN: I thought that was what was meant when you said the computer goes and finds out what he's eaten and so forth, but I was hoping it was true. Thank you.

DR. HEERINGA: Dr. MacIntosh let me return to you if you have additional questions.

DR. MACINTOSH: Not really, I have a few minor questions that I can pose perhaps rhetorically later.

DR. HEERINGA: Continuing with this format I would like to go to Dr. Hattis who I think has been nominated as the lead discussant for question 2.

DR. HATTIS: First there's a quick question for Dr. Chaisson on question 1 and it is are the residues -- you've got a lunch being taken of two different timesteps, you're keeping the residue levels

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consistent across the two timesteps for a given meal, right?

DR. CHAISSON: We made up some basic rules, but within a meal we're assuming basically that you've put the meal in a blender and you're consuming it evenly across that period of time, we couldn't get into the level of whether you eat your peas first and then you eat your potatoes.

DR. HATTIS: But the residue stays the same so that's fine. Paul, I guess you're changing -- I'm very glad to hear that you're changing the blood flow distribution as well as the overall blood flows in relation to the activity as a much needed set of changes to often what are more fixed patterns of PBPK modeling. And you're changing both the flows to the muscle with activity and the fat?

MR. PRICE: Yes. The idea of -- well, we've already gone ahead and looked at the equations over how to change the total cardiac output with general level of activity. We have had discussions with the PBPK modelers on a very general level that hey you know when you get active the extra blood goes to the

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muscle group to the poorly perfused category and it gets pulled away from the digestive organs and that these general patterns exist, we haven't actually sat down, gone through the literature, found the equations, but is our intention to do so.

DR. HATTIS: Final -- and this is a pretty big topic area -- is that you've got the variability that's captured in the model equations for these basic characteristics of blood flow and organ sign size, but in each of the equations there's an r squared value that measures how much of the total variability that you capture. Now it's a little bit of a touchy area to say okay, I've got some additional variability beyond that which is in the r squared, are you thinking of building a stochastic component to maybe build in a bit of extra variability that recognizes the fraction of observed variability that you didn't capture, that the investigators didn't capture in their models.

MR. PRICE: The short answer is yes, we've had a lot of discussion recognizing that using regression equations to capture the correlation of

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height and weight and organ volumes works great. There's some organs that are very well predicted and there's some age ranges where they're very well predicted, but there's some terrible situations, there's just no good prediction for brain size as a function of height and weight for adults and for lung size, tissue volumes for the lung, and that's just the physiological recognition they're not well correlated by them, and so there is a need to capture that variation. Fortunately these are organs that don't have a huge amount of variation, they don't act -- vary by factor of 10, so missing that's not a critical issue, but those organs would be best handled by some type of analysis of looking ad the residuals and seeing if the residuals are correlated to any given size or age and then sampling from the residuals to but that variation back into it. So we've had a fair amount of discussion about that and I think it is something that's very feasible to achieve in the future.

DR. HATTIS: And you mentioned that this is an evergreen system that you're continuing to

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re-evaluate issues, particularly issues like adapose (ph) fraction against new data as they emerge and are able to be evaluated, so you need to do the uncertainty analysis, you might want to have a

selected set of comparisons with data not used in the model derivations and see what the systematic and random errors are that you should be thinking about for the long term, not necessarily in this coming version.

MR. PRICE: We actually have a nice opportunity for that because the new NHANES physiology data has been released in the last year so we have a whole new data set to work with that was not available when the P3M model was done four years ago.

DR. HATTIS: I think Dr. Reed had a question about the use of the exposure factors handbook data for overall breathing rates for very young children like infants, and you have evidently chosen to use the exposure factors handbook's data which are a relatively constant level, am I right?

DR. REED: Yeah, the reason we have gone through and run the P3M and actually we were looking

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for a default or breathing rate or to revise our default breathing rate for children so I'm not quite sure and this will be my question, it appears that you were using these parameters from Latent's (ph) equation and one of the parameters, parameter A, the food energy intake divided by base metabolic rate number, it appears that you were using what was recommended by the exposure factor handbook for an H range of .5 to 3 years old, I think the numeric value is 1.6.

And since we were more interested in the younger age actually in the exposure factor handbook there is also a number, 1.9, for infants less than a year old and I'm not quite sure if you were using the 1.6 or 1.9, I am sort of back calculating, it looks like you're using 1.6, the value for wider range of age and I was wondering if you have any sort of rationale for using a wider age range than more age specific value and sort of the companion question with this is, did you make differentiation in this case for breathing rate between what would be the breathing rate if you were estimating for long term exposure

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versus short term, I would think that you would be more interested in using a short-term number and then the looks like for breathing rate you would have to take into account some kind of iterations of you know different values depends on activity patterns and how do you incorporate that?

MR. PRICE: You have asked two question so let me take a stab at answering both of them. The first question on the physiology, my memory is that we did use the value of 1.6, I do not remember exactly why we did it or the reason, I would be glad to look into that.

DR. REED: But that was actually exposure factor handbooks recommendation.

MR. PRICE: We very much followed the

exposure factor's handbook for the breathing rate equations.

DR. REED: And they packed them together in one group.

MR. PRICE: Yes. We're referring now not to how we would suggest that LifeLine would use these equations but the equations were used in the piece of

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software called P3M and in that range, that piece of software we used -- we followed the exposure factors handbooks guidance for the value.

And on your second question which is how would you revise LifeLine to provide the physiology to support a PBK model and there we would not use the Latent equations that are inside the exposure factor handbooks because those seek to derive a 24 hour average breathing rate that reflects a certain amount of time of sleep, a certain amount of time doing activity. What we would use and off the top of my head probably would be the modifying factors that latent had in his manuscript where he said here's your base resting sleeping level rate and then if you're doing light level you multiply the breathing rate times X, if you do heavy level you multiply times Y, you know different numbers for multiplication factors.

That's actually the approach that's in LifeLine right now to derive breathing rates that are activity specific so that if we have a person sleeping in a room and a bug bomb goes off in the room and they inhale a certain rate, we'll use the sleeping

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breathing rate, if we have the same thing where a child is playing in a room where an insecticide has just been sprayed but the child is playing we're going to use an active breathing rate and will tailor it to the activity, that's already in LifeLine, we see that framework as being extended to this 10 minute status where we would say what are you doing now, what did you do in the previous 10 minutes and what does that say about what your breathing rate should be.

DR. REED: So a follow-up question is in terms of the seamless merging from the exposure to the PBPK model for this particular component model you're not using the P3M data because --

MR. PRICE: We would propose to do something better than what was done in P3M.

DR. REED: And you would incorporate that into your exposure estimation and not when the data is moved into PBPK model.

DR. CHAISSON: And we have one extension on that, the same theme, Ruby, we have already programmed in another set of LifeLine software that's not the topic here today but for subpopulation exposures and

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we've taken a look at what we call disease limited activities, for example asthma, let's say X percentage of the children between certain age group are

considered asthmatics then those breathing rates should be changed.

And now I personally think that the approach we've taken is relatively crude but we've at least have opened up the door and it allows the user in the software to say X percentage of given age range is asthmatic and it's going to use a higher breathing rate per -- then would have been normally attached to that particular activity pattern, so that already exists and what we would like to do is employ that now in this next way of software, we've already sort of experimented with that and that seems to be working.

We're not satisfied however that we necessarily have the right dynamics built into that and we will be looking into the literature or hope somebody might be able help us decide exactly what kind of adjustment if you will be made for asthmatics which might be different than the adjustment that you make for some other disease limiting -- or disease

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activity changes that were related to a disease date, diabetics is another issue.

DR. CORCORAN: I believe this would be directed to Dr. Price, and I'm going to just limit my questions to the P3M model paper which first of all I would like to commend the group, begin by commending the group, I think this is massive effort and it is a large advance for the field and also commend the group based on your candidness regarding where gaps exist in data and in the scope and range of the model. But nonetheless these gaps do exist and there are limitations and I have a couple of questions and I also realize this was work that is probably now more than two years old and there's been advances made since including some of your responses to Dr. Hattis in addressing variability that's not captured by those who are the outliers in the -- even under circumstances of high correlation coefficients, but perhaps you could let the panel know your current thinking or ways you hope to address some of the gaps and I know you're final disclaimer you're hostage to the literature, if the data aren't there you're

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unlikely to be able to generate it yourself so you have to operate with what is published and peer reviewed and accepted.

But perhaps you could tell us a little bit about your thinking in a couple of areas particularly filling some of the high priority data gaps that reflect sensitive subpopulations particularly the very young children between the ages of 1 and 3 seem to be a challenge for your regressions and you're thinking about that high risk population.

Secondly would be the physically minor organs but perhaps not functionally minor organs which account for five percent of the body mass of men and ten percent of the body mass of women. I know again

there's very little data on blood flow to the reproductive organs and others but they are a very significant concern in terms of the protection of human health and that would be an area if progress could be made I believe would be a very important contribution.

And I got a third thing and I hope I don't confuse and you by asking three questions and if you

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want me to stop and hold off before the third one I would be happy do so, if you want me to proceed I'll do that as well.

The third issue is the data sets which you had, you're privy to were significantly deficient in some other important areas other than the two I've mentioned so far, they would include one that was surprising for me to see and that was the elderly, and obese individuals, pregnant individuals, and individuals with other significant comorbidities which Dr. Chaisson already alluded to for two important comorbidities. I know that this just grows expedentially with each of those comments and there is limiting computation power in the universe, but those are just a few of the areas that in assessing the P3M paper which I want to return to the comment and my belief that it's a tremendous, this body of work, it's still a work in progress though.

MR. PRICE: Well its that's one of the reasons -- all of your comments were one of the reasons why I put out that it's an evergreen project is that we regarded this as being we had a significant

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amount of funding which is as I said the American Chemistry Council provided to us to get the project started and for all the reasons you described, the data gaps we discussed, the data gaps that happen for particular organs that you care about whether it is reproductive or so that the GI tract organs turn out to be very poorly done as well, or it's age ranges where I have a hypothesis that it is very easy to get infants underneath the age of 6 and it's very easy to get infants who are at school age but there's a gap in between where it's hard to put cohorts together to do the studies and because of that there's just a weakness in the literature of reported models of changes in organ volumes during that age range, and then around puberty it's just a mess because so many kids are changing so rapidly at so many different ages it's just a hard critter to model and there's so much variability going on, so those are two age ranges and you can see it in our results ages where the models don't do as good a job as they do with adults .

For all of these reasons it is really a work that needs to be continued onward and we would be

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delighted to see work for supporting the PBPK modeling as it being another avenue to move this exercise

ahead. The second area where it's really exciting is that when we looked at the number of papers that we cited and the dates at which they were published 70 percent of them were less than three years old, it was just a tremendous expediential increase in the amount of data that's available and it's coming because of better computer, better training, and better diagnostic equipments, the MRI's, the CAT scan based technology to institute organ volume measurements for a large number of people because the costs are coming down. It just makes a tremendous field to keep focused on.

DR. CORCORAN: And as a corollary question is there anything you believe the Agency could do that is within reach to help address those specific items that I addressed?

MR. PRICE: Before I answer that Dr. Chaisson would like to talk about some of those subpopulations you've talked about which is an additional dimension.

DR. CORCORAN: And before Dr. Chaisson if you

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would permit me one last thing is and this again is perhaps a structural and a philosophical issue even when one obtains a correlation coefficient squared of .9 the most important individuals might be those actually who fall out who are the outliers in that correlation and they may actually represent the sentinal humans for pesticide toxicity or other events, adverse events and while the high correlations bring great comfort there is also the concern that there's a false level of comfort.

MR. PRICE: I will be glad to respond to that.

DR. CHAISSON: There are a couple of points that in your three questions that are sort of link and these are topics that I'm particularly interested in and that gets into the issues of subgroup analysis and some of the disease states they said that we had been looking at for the last two years which probably changed some of the parameters. Paul just briefly mentioned issue if you're looking at PBPK and this isn't relevant I assume to carbamates but maybe in the next group where maybe you have a subgroup where the

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enzymatic focus is ethnically related in terms of its competency for example or you have a particularly sensitive subgroup because of something that's going on that's related in the PBPK, so I think it's time now that we have to get these models to be mature about looking at subgroup and subgroups can be defined if you will in a way that deals with things like breathing rates and things like disease modified activities or rates involved with that.

Two of the areas that we've looked at which had to do with obesity and asthma -- by the way, the field of obesity research has exploded now we haven't been funded to go out and do the P3M kind of thing now

but I'll be you if we looked now there would be all kinds of stuff there that was just not there a couple of years ago, but having said that there may be in fact the correlation between some of these situations and age or some of these situations and socioeconomic groups or some of these situations and ethnicity or whatever and that linkage I think we've got the right pieces in the model but we don't have them linked now, so we kind of duct the issue by allowing the user to

put in the numbers and make the linkages, that's because we don't know what the right answers or what the linkages should be, but I'm convinced that once we start looking at the literature that we're going to see linkages like that and those may in effect become surely for the PBPK work it's going to be critical for us to at least have the model be flexible enough that when we see that kind of a correlation that those correlations will be offered up to the assessor so that they can employ them.

And we certainly have seen that in the tribal groups with the obesity and the asthma and those were both age related. And some of the things that I saw were quite startling and so we -- like I said we started to develop the models and we think that we've got them well enough along that when we do this one we will be able to employ those techniques and bring that in.

MR. PRICE: In response to your question about the sentinal individuals and the outliers, as you indicated before we are hostage to the literature and the hostage crisis gets worse because we're

hostage to what people choose to publish about their data and quite often the things that they don't want to publish are anything beyond their regression equations, they really do not like talking about their residuals or releasing the data even when we contact them and ask for it politely and indicate we are non-profit and we are using it for open software, but we get great reluctance for people to release the raw data that would enable us to do that analysis.

How could government help, I think this is a fruitful area for research and that resources given to this area and a framework to collect and organize data would be a very nice near term project to improve that the start that we've made in the P3M process.

DR. HEERINGA: Dr. Reed, I believe I cut you off just as you were about to ask another question, I will give you that opportunity.

DR. REED: Thank you. I was just going to ask a follow-up question to the inhalation, the breathing rate question that I have, similarly for other parameters that you have in P3M a lot of them were again lumped together in terms of age group and

all of that, do you think that there might be

sufficient you know data to you for part out like you know 7 to 14 years old, part them out to smaller increments of age.

MR. PRICE: Well let's be clear over what P3M did, it said that -- we went to the literature and we said four particular organ volume, let's say it's kidney, out of the published literature you can roughly assume that people who are still growing are different from people who have reached maturity and so we automatically care that adults will be different from kids, so you go to the literature and say who has done, the people who are adults, who has done children who are actively growing around puberty and getting the big growth spurt and who are the ones that are looking at infants and then toddlers, those are kind of -- you go on a base set of assumption that those are kind of the age groups you're looking for and you looking for who has published studies of those age groups and sometimes you find them and sometimes you don't.

When you find them and let's say someone has

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done an age study of 12 year olds to 20 year olds, that's a typical age study you'll find, you will get an equation that comes out of that study which shows a certain r squared against height and weight and if that equation is applied to 12 year olds, well the height and weight of 12 year olds are going to generate organ volumes that will be specific to 12 year olds, the same regression equation would apply to 20 year olds, will provide numbers for 20 year olds.

So event the study is over the gross time scale it actually produces estimates that are age specific, maybe not ideally but they're a little bit finer than the kind of gross blocks. I think that's about as best we can do at this point relying upon general studies.

DR. EDLER: Actually that was (inaudible) what we had discussed yesterday when we had the carbaryl risk assessment and where we struggled between the MOA for the administered dose and the MOA for the internal dose and so the question arises just for this interface that you had shown the one year slides where you told us this interface must be very

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seamless just that you don't get interaction or get wrong things on so the question is a little bit where we end with exposure and where we start with a pharmacokinetic model.

So is there a possibility to put various internal exposure actually located in the whole modeling, it's part of the exposure model or it's part of the pharmacokinetic model.

MS. FRANKLIN: I can start the comment on that which was really the purpose of the slide that I had put up and I think the comment that it will be very important for there to be a good interaction

between the people doing the PBPK model as well as the ones doing the exposure model. We can provide the information that would be the amount of exposure at a contact surface and then it would be the PBPK modelers that would then say what's the flux or the percent absorption or how does that get into the system and then they would do whatever the distribution would be to the target tissue.

Some models may actually want a number that's even further back than that that's either the

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concentration in water, they would then put the intake parameters on that and then they would put the absorption parameters. We're trying to build the exposure side so that it would accommodate the metric that the PBPK people would want, we could take it as far down as they would like or we can take it as far back.

Now that may become mute as more models are developed and it may turn out that is more effective and efficient to have the data entry from the exposure be taken down to perhaps this final level or as an absorbed level, but I don't think the PBPK models are sufficiently standardized that I think it would be dangerous for us to build it that we could only put this out in one parameter because you have undue an awful lot of the work to try to get it to that particular stage.

But I mean if we're missing a data output that you think would be useful that would be helpful for us to know that, we've gone with I guess are the more traditional ones that we're aware of and would certainly be able to have the equation take it down to

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whatever point would fit.

DR. EDLER: Just for clarification, that means are you telling us that there may be final and different models for different models where you -- or different interfaces between exposure and pharmacokinetics for different substances and so or sometimes could be the internal dose part of the exposure model sometimes it makes sense that it's not part of that?

MS. FRANKLIN: That's correct and I think that's partly because we anticipate seeing -- we're optimistically anticipating seeing development of PBPK models that would be not necessarily just for carbamates or for pesticides but could be for other types of chemicals, and so what you find is that the people who do pesticides are not necessarily doing things exactly the -- does not mean I'm talking too much -- their not doing it exactly the same way so that I think it makes it very usable for a wide range of disciplines, this was Claire Franklin.

DR. HEERINGA: Thank you very much. I'm going to do go to Dr. MacDonald and back to Dr. Sohn.

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DR. MACDONALD: I have two questions which are a bit different from the ones being asked so far. First of all I suspect I am not the only person in the room who would benefit from an explanation of your graph options for filtering, in particular my questions are what is the X axis, is each person on the graph three points meaning a total 10,000 persons so there are 30,000 points on the graph, and you have been accumulating exposure over what type period in this picture or does it matter?

DR. CHAISSON: In this particular picture the X axis each notch is a person, there are 10,000 people, each of those particular dots if you will are seasonal averages for an age group, now that's distributed -- I'm sorry, that's not true -- this is one age group, this is one age group and I don't remember what it is, it's just an illustration, but the point of this was that on the X axis you have people and each of the icons or each of the symbols I mean above it is either food which was the dark blue triangle, residents which was the green and drinking water which was the light blue triangle and what this

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is saying is that the exposures for a given person are broken out here in terms of the exposures that came from the residents, the exposure that came from the food, and the exposure that came from the drinking water.

Now we could have elected just as easily to have said show me only the exposures from the household and order those from lowest to highest in which case the curve would be different or we could say well gee I'm really only interested in food in which case those other ones wouldn't -- or gee I just want to really know the total, I don't care what the source was or the route of exposure, and so the program lets you slice and dice it however you want.

At the end of the day however you end up with some distribution starting in this case at five orders of magnitude difference because the Y axis here is in log scale of exposure. There were in this case for this age group there were what probably 15 to 20 percent of the people saw no exposure, but once they saw exposures you had five orders of magnitude difference in the exposures if you looked at total and

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they went -- now there's something different about what's going on with the kids here who didn't see very much exposure versus obviously the ones who had five orders of magnitude higher, that might just be their exposure opportunities, I don't know, but the point is that you can go back and take a look because each one of these individual's records are now available so you can see how come there's a difference.

If you're doing PBPK maybe you're interested in the people along the course, maybe if you're doing this for regulatory purposes maybe you're just

interested in the upper 2.5 percentile or 1.01 percentile, whatever, so my point was just that once you show is distribution of exposure and for each on that exposure you have maintained -- you have tagged that value with all the demographic and ethipomorphic (ph) and everything else information that stayed with that number all the way through so you can point at it, you can find out what's going on and that's what's being delivered to the PBPK model.

We're simply saving it's not for us a modelers to hard wire for you what -- this is our

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philosophy -- which of those points you should transfer over to the PBPK, but that the person who is doing the assessment should be able to look at this and say okay I want this model to deliver to me all the information about fill in the blank here, only the top guys, only the bottom guys or people in the middle or every 15th person or whatever and that's going to be dictated both by of terms of what's of interest and somewhat of how much volume data wise that the PBPK model can handle, so if you've got a PBPK model that can only handle a hundred people you're going to have to pick from that which people you want delivered.

And my point here was just to say that there are many options for this and that we're going to make the interface such that the user of this information will be able to select the individuals that are carried over.

And the other point was that the user should really understand what's happening because you are leaving people behind and that might be important too, you don't want to accidently leave people behind who might be the outliers or maybe there's -- you should

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really understand what you're leaving back there as well as what you're transferring over to the PBPK model. And that's another reason what we're talking about it transparency of each of the pieces that goes along there because I think it's very important to understand what you're not bringing over to the PBPK model.

DR. MACDONALD: I have a follow-up to this question and then I have another question.

Have these people then ben ordered by total exposure and then the there's a solid line at the top is that there's a lot of people for who their exposure is almost entirely food and others for whom it is entirely residential.

DR. CHAISSON: Dr. MacDonald, I just chose one slide, you could with a push of a button reorder it, you could say reorder this in terms of dermal exposures, reorder this in terms of food only. In other words you could pick your parameter on which you want to create that distribution and it is a push of the button, you have this huge data block in there, you've already done the calculations, they're sitting

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there and you can just tell the computer I want to see it differently.

So you could have created -- we could have just created exactly the same distribution based on some other parameter and then but that is exactly what the -- what we're doing again and so the user can say -- I'm just going to do a hypothetical -- that for whatever reason you're interested only in inhalation exposures to be transferred over to he PBPK well then I would tell the model output reorder this in terms of the only inhalation and you'll get distribution from low to high, just the inhalation exposures and we'll throw away the food exposures or we'll throw away the oral, we'll throw away the dermal and then you're still going to end up with a distribution of people who re attached to those exposure numbers, and then let's say that's 10,000 people, the PBPK model can only handle -- I'm going to pick a number -- 200 people so we're going to decide which 200 out of the 10,000 gets transferred across.

In making that decision we want to provide an option to the assessor to pick whatever people they

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think are important and they can do it randomly, they can do it -- maybe one of the options can be randomize it, one of the options can be give me every person. And my point is just that we don't want to hardwire this so that it only delivers a given set of people.

DR. HEERINGA: I believe the panel will have recommendations on exactly how to provide those types of option.

MR. VOICE: To finish up with that when the graph was introduced it was introduced as typical LifeLine output and I think most of us needed a bit more and that what you said was very helpful.

The other question concerns something that I'm always going on about but what's the ongoing quality assurance for the coding of LifeLine. In the past we've seen actual code at the panel and we've reviewed that but it's now a bit of a monster in a package, does it ever crash, if it crashed do you know what the makes it crash, what's the chance that there are coding errors deep inside that means it gives plausible results but not the results it's supposed to give, what's your ongoing QA in the development of the

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program.

MR. PRICE: The QA program for LifeLine is built around delivering the model and listening for bug reports, so let me talk about it in those two phases. As we develop a new version of it we have a formal process for testing the model to testing the outputs against -- an independent way of predicting the outputs to confirm that the various algorithms in the portion of the model are operating in a way that we -- that makes sense. After we do our analysis it

is provided to EPA and people who have not been involved with the training development to LifeLine up to that point then test it and test it to see does it work, does it give answers that make sense, does it do what it's supposed to be doing.

And that data analysis is part of the process releasing new version, so that when version 2.0 came out it went through that process. Then once it goes out we have our phone numbers and we have our internet site plastered all over it with instructions that if people have a problem and there have been a number of people who have reported they have a problem or

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something is it working right and with models this large you can't test every option in every way and every data set that's in there, you really at the -- it really depended upon the user to come back and provide you the feedback and the guidance and we have been getting feedback back and some of the things we're able to correct and put out minor modifications for, other ones we're kind of saving them up and a bunch of them will be addressed when the new version comes out, so we had that process for handing QAQC.

If we're talking about the work we're here for today we're presenting a white paper, the work for this has not begun yet, when it does begin it will go through the same sort of process and we also have the option in our existing models that there are other models which you can now do intermodal comparison and at this point I may turn over to David who might talk something on that point.

MR. MILLER: We routinely run LifeLine as part of our risk assessment process, we also run deem (ph) and we look at comparisons, compare the two and generally they're quite comparable, and then we've

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also have done a model comparison workshop before. As far as crashes it works well, there aren't a lot and yeah, it's a routine part of what we do.

DR. SOHN: This goes back to an earlier question about discussion about timesteps or so, I want a point of clarification, the PBPK model is going to be dynamic, is that correct, is it time dependent or is it going to be static intervals of steady state?

MR. PRICE: We're providing the input in the form of these timesteps where for each timestep there will be a single dose, that will get turned over to the PBPK modelers and it will be up to them to find the most optimal way of using that data and I've heard informally back that it will vary from model-to-model but the techniques you talked about are certainly on the table and have been incorporated into models.

DR. SOHN: Do you perceive any case where you're going to have to retool your output in the case of a dynamic PBPK/PD model?

MR. PRICE: Because they're not linked because we're delivering an output file which would

then subsequently be used there's not way of putting a
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dynamic feedback loop into it, but what we envision is that the user will come to LifeLine and will say I want to generate data that will support a PBPK model.
The timestep I know you can't do it any finer than ten minutes, but my timestep an hour is fine for the time things I'm measuring, so I'm going to set the timestep up for one hour, but I care about seven days, not one day, and so the exposure history will be to find seven days, one hour, 24 times 7 timesteps and will generate that for individuals.
So it will be tailored to the needs of their PBPK model, and then they will go through a check off list and say fatty tissue is not relevant for what I'm doing, smooth muscle is very relevant because that's the target organ and the liver is relevant because of metabolism and there's not inhalation or exposure so I'm going to turn of inhalation and I'm just going to worry about cardiac output, and so they preselect the things that they want and only those will be generated for the output file.
And when they actually take that over they may well do all sorts of interesting things to even
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generate finer timesteps with the understanding that they go to a timestep finer than 10 minutes the burden is on them to make the assumption over how the doses apportion, but they may want to go and just do an assumption that maybe it's uniform across that timestep or some other assumption and then the have the freedom to set the timestep whatever makes sense in terms of the PBPK model.
DR. SOHN: The one last point of clarification, I think we've discussed this issue of variability in terms of aggression model and we use term outlier, before us statisticians go crazy here, they're not outliers, they're actually just people that are missed from the accuracy of existing regression model, so we should be concerned about.
And our squares aren't variability that's just deviation from the model, so I think you should be concerned that just adding or incorporating the air from the r squared does not necessarily in itself incorporate variability in the actually population, that's my only point.
DR. HEERINGA: Historically that term outlier
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probably was a bad choice of terms, outcast or anything like that.
DR. PORTIER: I was going to say the politically correct statistician refers to those as influential observations, all right, so we will refer to that from now on as influential and for exactly the same reasons I mean they're going to influence the risk assessment because those are the individuals who are going to drive the tail of the distribution for

the most part.
I did some -- this is clarification -- I did some back of the envelope calculations, if I calculate one day for 10,000 individuals we're talking about 14.4 million records of the table 2 type, if we calculate one life time, 72 years, of information of -- and that's records, right so that's 14.4 million records, if we do one lifetime for an individual that's 3.8 million records, and if you do 10,000 individuals for one year you're talking 2.8 billion records here, so the data sets that can come out of here are huge I mean 2.8 billion times the number of columns in that data set will make a significant dent

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in my hard disk.
MR. PRICE: We are the reason why hard drives have gotten very large.
DR. PORTIER: Of course that's today and in two years we will have terabyte, but my question comes more to whether LifeLine is in a -- programically is in a situation to be run in a parallel environment because some of this, we might want to generate 10,000 individuals one year exposure on a 10 minute basis that's not unreasonable, but I may not want to do that on my home computer even at 2.5 gigahertz processor speed so I wondered -- I think the answer is it's maybe if we work hard enough.
MR. PRICE: We have tried to adhere to good software development practices that would follow the guidance of Microsoft on how to make a well behaved program and part of doing that is to enable the software to easily adapt to be running in a distributed system, we haven't actually tried to do incorporate those things into the model but we've looked ahead and said that some people may want to use LifeLine in extreme fashion such as you've just

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described and to generate large data and we'd like to have something that's amenable to those type of analyses, but have we really gone down that pathway yet, no, we've looked ahead and want to make sure it's an option though.
DR. HEERINGA: Just to clarify then your policy right now is to develop LifeLine and potentially this linkage to PBPK modeling for standard microcomputing-type accessible platforms not necessarily to high end computing environments which could obviously accommodate faster processing speeds and greater storage requirements.
MR. PRICE: That's correct. And my apologies to the MacIntosh users we are limited by funding to just deal with just Intel machines.
DR. HEERINGA: I do notice that these panels are just filled with Mac users.
DR. PORTIER: I wanted to follow up on the comments made by Dr. MacIntosh, Dr. Ryan, and Dr. Sohn. When I look at the output from table 2 what I

see is 144 point discreetization of the exposure function for each of those components, so in is sense,

David, if they could do it as differential equations you would get the form of a function but in this case they're giving you 144 points, a numerical discreet integration of those functions which brings up the issue of why you hadn't thought about actually taking those about 144 points and then summarizing them in a functional form or trying to somehow compress them down and actually deliver a function instead of delivering a 144 points, that would certainly compress this down a lot.

DR. CHAISSON: Good idea.

MR. PRICE: There's lot of merit to it, we haven't followed it as our base case because of the difficulties in maintaining correlations that you can for a 10-minute timestep be able to say that this 10-minute timestep happened at the same time as all the other parameters for multiple chemicals, it happened at this timestep and the linkage across chemicals is easier to handle if you keep them as discreet rather than trying to summarize them as a function, but obviously there are ways when you have this much information there's great value in finding

strategies for simplifying the data and handling it in a faster fashion.

DR. PORTIER: And I was thinking not so much internally but in this external table that you're going to be delivering to the next component which is the PBPK model in whatever form it is, I mean if you gave me a function and I can redefine my timestep for whatever it needs to be for my next function and these tables already incorporate your correlation structure that you built-in from your food use, your residue use, your activity use, I mean that's already built-in, you're just telling me 10 minutes into lunch this is how much a dose is going to be delivered in the stomach, this is how much to the tongue, you have all those components there already built out and I haven't thought it any further than that either.

DR. HARRY: The one question that I have is that you know a model or any software program is only going to be as good as the data that goes into it and while it will not be your responsibility to evaluate the quality of the data that is presented to you or it shouldn't be, but my understanding is when you have

the curve up that you said you could basically click on a unit and that could bring you up the record for that person and then we have the old outliers, whatever -- the influential observations, there needs to be some way a person that's trying to model can go back in and have confidence in all of the data set that they're doing, so rather than trying to identify quote an outlier because though studies may actually

fall right along the curve but's it's not a high quality study, has it been thought of any type of strategy that you're not necessarily making a judgment for the modeler but that they could get something more than having to individually click on each person to see what the record looked like.

DR. CHAISSON: We call this data pedigree and it's a problem. We have a full range of stuff that we use in these models and it ranges from really extraordinarily robust contemporary wonderful data to something we call professional judgment, it lays in there with your informed observation, but in our technical documentation first of all we try to clearly tell the people the difference, where we think we have

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a great data base we talk a lot about it, we show what's in there, we show if possible how the data were collected and whenever, CFSII is a good example of NHANES is a good example.

In other areas we use default values, assumptions, distributions of assumptions and we make it clear that this is our professional judgment and we give you the opportunity to actually go in and change the number of your professional judgment is a better pedigree than my professional judgment. Unfortunately some of this gets lost if people -- you're assuming they're going to read the several hundred pages of the documentation -- when you click on the person you can actually go back into the record you can actually look at the data record that was chosen, so you can actually say CSFII record number 264 was used as the basis for the dietary piece and record number 67 from NHAPS (ph) or whatever is actually in there, so at least it gives you the genesis for the calculation and then I suppose it's up to the user to try to establish whether or not there's something unique about that data base from which the record was pulled that would

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be inappropriate for the question that's being asked in the context of that exposure assessment.

This is I think a very important thing, I think it is one of the reasons why we harp on this idea of transparency and we don't know how to build models with only good data or without assumptions and so the only thing we know how to do is make it transparent as to what information is going in and then make the data -- we hope that the data can get tracked back to the input values and we're very much open to suggestions.

As we go forward and these models become more complex like this that issue becomes even more important, and it's not just the data by the way and the other thing I like the harp is it matters how the data are structured and ordered within the model. You can use the same data base that I use and we can come out with very different answers, depending upon how I bin my numbers and how I order and structure them, so

it's just as important, you can start off with a study that's a spectacular pedigree and then screw it up in the way you put it in there and you end with a good

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data set that you've abused in putting them out.

Or on the other hand sometimes we like to think that by combining data in a very orderly fashion that you know the sum is better than the other two pieces that went into it, so I think it is important to know how the data were used within the model just as much how good the data were in. We are very open to suggestions that the panel might have, as we go forward this is going to be more complex, it is very important as we tried to say that the user understand what's not -- not only what is being transferred, what's being left behind and why and how this data were calculated.

DR. HARRY: I'm trying to think that if I was not doing this but if I was trying to look at a model or any set of data where I'm looking at different sets collapse and somebody is expecting me to look at the electronic version of the data basically there is there anyway, and I don't know if this is worth doing or not, but is there anyway that you could say could I cluster these data sets to say even a color-coating type thing about if I saw the scatterbrain going

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across if you had all of the people on there, if that was color-coded on a basis of even the bins that you said that you put it in when you have your pages of instructions, you know this is limited by a small study or this is a large study or anything like that that could take the person's eye sort of as a red flag to say you really want to go in and look at this type of thing, if there's something that almost in a way makes you red flag them to say when you're looking at all of this realize they're not all the same and you might want to go in and if you start to see a clustering of color somewhere then you might want to go look at that.

DR. CHAMBERS: Dr. Chaisson, you answered the question earlier about if a meal extended over more than one 10 minute period then you blend it, does that go the same for the activity periods, do those go over several time periods, do you link to the same residue scenario?

MR. PRICE: Yes, I will jump ahead and answer that. The idea is that an activity pattern specifies the start and end time of a block of time for the

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macro description of the activity, where you do it and what generally you're doing, and it will be a much courser time 16 scale then the 10 minutes, so yes you could see from my flow charts I basically made the assumption any time in a period of time it is safe to assume you're going to be one activity in one microenvironment, and exactly what you do there and

how you handle a variation across that block of time is an area of intense research at this point and we would me very much desiring to harvest that research as to say what are the strategies, for how do you say okay I'm only on a 24-hour block of time then the assumption about 20 hand mouth events per hour isn't an unreasonable assumption of that time scale of one day.

Now I want to care about it down on a five minute time scale or a ten minute time scale, can you do twenty hand to mouth events in 10 minutes or is it limited to one or if you do them does it really count because if you don't recontaminate your hand, just keep putting it in your mouth that doesn't really -- there is a great need to revise the non dietary

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exposure methodology when you go down to this finer time scale and we're very interested in harvesting that but we do not claim that we know exactly how it should be down.

DR. CHAISSON: Dr. Chambers, you brought up another point which we didn't really get into except very briefly and that was about defining the duration of the activity patterns. Because of the point you said that for example on the slide I had a person playing golf and eating a snack and so okay snack that's easy to say it's the sign of 10 minutes, if it took him 8 minutes or 10 minutes it really doesn't matter, but now they went out and played golf and they're out there for two hours, three hours, or six hours, and if it's a unit of exposure and you're going to amateurize it across those number of hours and obviously the dose that's delivered in any 10 minute interval within those is really going to be dependent on your decision about the duration of the activity patterns, they're sensitivity, it's really almost more -- there's much more impact on that decision than there is then whether it took me 8 minutes to eat

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lunch or 13 minutes to each lunch.

So that key is very, very much something I think we should be making sure that when we come back hopefully we'll come back with the model that you pay attention to how people have decided that will be somewhat subjective. We are going to have to walk from one data base to another, we will have to look at a data base which perhaps -- the other day I was looking very carefully how chads for example look at the durations and some of the activity patterns and how they derive those numbers, we're going to have to employ something like that to make decisions and I suspect that people will have an attitude about whether that was done correctly or not but it does have an impact on the delivery, the dose, and the 10 minute intervals.

DR. HEERINGA: Just kind of an update for everybody for what I anticipate on progress here, I

think we're making good progress with these questions, I don't want to limit them but I realistically if we're going to stay on schedule today, if we use about 15 more minutes maximum for questions hopefully that will accommodate it and do the public comments before lunch, have a short lunch and then probably return here at about one o'clock to continue with the questions. I'm thinking out loud a little bit today as I said at the start of this meeting I want to make sure we stay on time.

DR. FREEMAN: This is a follow-up to what you were just saying about the 10 minute intervals. How would you deal with a scenario where a child is snacking on a banana and moves between microenvironments which have in themselves different environmental contaminate levels, but what you're looking at is you're looking at the dietary or the non dietary, however you want to handle it, handling the food as you walk through space activity, because the way I understand it what you have is you've got discreet locations within which discreet activities occur, but activities that's not what happens in the real world, the activities may go over many different locations but it's still the same activity on some level.

MR. PRICE: The issue you're talking about here is the inability of macro scale time activity diary records or diary tools to capture the reality of how people eat and move and breathe and change microenvironments on a moment-to-moment basis especially in certain age groups, that's a problem which I don't think we are able to solve inside of this exercise.

We're building from a record based approach which is really therefore contingent upon these large surveys of activity patterns on the macro level. I think what we would like to do is to try to be as intelligent as possible to try to address these problems and how we parse out a big block of time and so instead of saying make the assumption it's uniform taking data that says how does a child's variation occur over a block of one hour, does all the exposure happen in 15 minutes or 40 minutes, is it nothing, is it always even, and to take that type of information to perhaps put in some type of variation model that would enable us to more realistically capture the short-term variation of true exposures that happen for these non dietary events and get into what you're talking about, but that's really an area that we're looking forward to explore, we think we got the model framework that could handle it, the trick will be trying to figure out how we can best mine the data on exposure assessment to come up with a transparent objective way of doing it.

DR. LU: I have to say that I'm kind of pleased to see this (inaudible) make available by LifeLine. The paragraph asking the figure 6 on page 49 that has exposure box, you have a PBPK box and there's interface box, to me is almost impossible to model those micro activities especially if you look at carbamate groups they have such a short half-life, you only catch every single exposure scenario, it's almost in possible, so I would like to offer a reverse thinking and then since this is part is waiting to be taken off you might want to think about this alternative.

I'll give you a hypothetical exposure scenario, a kid that just ate eight cherries which happen to have carbaryl residues on it and then he went out to the lawn to play for 30 minutes, the lawn

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has just been treated with carbaryl, now you're going to get all the activity information, all the residue information on the food and it goes through the data, the exposure, the aggregate and cumulative assessment models to generate a number that can be used in PBPK model, what happened is if the researcher can collect that spiral (ph) sample after the playing on the lawn okay and send the sample to analyze for the metabolites (ph) which has the detectable level how are you going to use that data, if that's available how would you use the data.

If I look a figure 6 here the data actually will be direct input to the PBPK model which I don't think would be feasible, practical, so I would suggest that actually you isolate the interface not attach to your exposure model, but treat that interface as independent and that interface take care of this urinary metabolite data, so you would convert to the level comparable to whatever will come up from your cumulative aggregate exposure model and that number will fit into the PBPK model, so that's just my suggestion.

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The other suggestion is that if we have to go through this micro activity or residue survey route and now we don't have any data available according to case uncommon which is true, but I just want to let you know that EPAORD recently funded three (inaudible) that actually require those research projects to (inaudible) human behavior data, so I will encourage the model developers, agencies, and those project PI to sit down and have a dialogue.

I mean those are the grant, I mean they probably won't do everything you want them to but I think a dialogue among those three groups will enhance the quality of the theater in the future, I mean not the deadline for the EPA but you know you will be surprised that if everybody is on the same page the quality of the data will be significant improve maybe in three to five years.

DR. CHAISSON: Thank you.
DR. FRANKLIN: If I understand what you're saying you're suggesting that we could use urinary concentration as one of the exposure outputs, that's very interesting and if you're able to encourage your

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colleagues to get information I, know I tried to this years ago when it's actually quite interesting because of course when you're looking at exposure to workers it's always a bit of a challenge because you're basically modeling a contact exposure to try to get an internal dose, it always struck me as being more reasonable if you knew what the metabolic output was is that you could work your way back in that way rather than in that way, so I think it is a really useful parameter, I'm not sure there's a whole amount of data that we can actually utilize for that, but it's I think something worth considering for the future because I think it really does give a much better estimate.
DR. LU: Just a response to that, considering carbamate group is such a short half-life, I mean I don't think that you will be able to catch the moment of exposures, the only usable tool will be finding integrate, time integrate and route integrate samples to get a model and unfortunately that's probably the fact. I tried this comment in yesterday's session and I want to say that again, to convert a urinary data to

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some sort of a comparable data requires some human pharmacokinetics which I think restauranteur the bear (ph) is doing this kind of work, so again I want to emphasize that this a project that would be taken off so you may want to consider that gathering those human pharmacokinetic datas and once you have those data is a matter of reverse calculations and input urinary data as the default numbers -- sorry not default numbers, sorry, dependent variables -- and those and default numbers will come from the pharmacokinetic parameters and that data alone I think, I mean I could be wrong, the quality of that data would be much better than all the guessing and assumptions.
DR. HEERINGA: At this point in time what I would like to do is one final call if there are any pressing questions, any pieces of information, obviously during the actual response to the questions this afternoon if we require clarification you have the opportunity to request that.
DR. REED: It is a very short question, Ken was coming up with this however many billion records that's related to one of the questions that we're

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going to be addressing this afternoon, just curious with 10,000 records 10 minutes one year, how long does it take for running such a model?
MR. PRICE: Well after we build it we'll know, but the short answer is that there are a number

of technical strategies for managing speed and complexity inside of software, we've used them in LifeLine already, we haven't done them on time scales of 10 seconds but we have modeled successfully 100,000 individuals for 80 years modeling multiple routes of exposure, and have been able to find strategies for managing that type of information, it kind of goes beyond what we're doing here but we've got some excellent ideas of how it can be done in a feasible fashion.

DR. HEERINGA: Mr. Price, over the next two years do you see a technology say at the desktop computer level it would a leap more than just increased gigahertz, I mean leap in terms of what could be done would change the way you would approach the programming structure?

MR. PRICE: It is not really my field of

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expertise, we're not banking on any great new creation of technology, we very much expect that the LifeLine software in order to be useful for cumulative assessment has to be something that can be run on a Pentium 4 with 10 gig, 20 gig hard drive, the type of bottles that you could go out and purchase today at a computer store.

DR. CHAISSON: If you look at it from the other side what's the worse that could happen, the worse that could happen is that we end up with sort of two versions, one is something that you have to link online and use for free online because you have to plug into something that's bigger, but for most every day kinds of things there will be a version that's compatible easily to the PC, and then you know if once in a while you have to dial up and get into something more powerful that can be accommodated.

DR. HEERINGA: Thank you very much. At this point in time I would like to move onto a period of public comment and we have two public commenters scheduled and I think if each of them would agree to keep their comments to about 15 minutes we will all

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stay on schedule. If there are any additional individuals in the audience who have not spoken to either Joe Bailey, the designated federal official or to Larry Dorsey (ph) who is executive director, secretary of the SAP, about the opportunity please try to do so now, we want to give everybody a chance to speak who wants to speak, but if again please see Joe Bailey if you would like the opportunity to speak and haven't been schedule to.

At this point in the order that people have approached us I would like to invite Dr. Jennifer Sass from the Natural Resources Defense Council.

DR. SASS: Good morning. My name is Jennifer Sass, I am with the Natural Resources Defense Council in our DC, it is an environmental nonprofit group here in Washington, DC. I am a scientist with the public

health program and I thank you for coming, it's been a long week for many of you and I'm sure it will be a long day for those that came in for this meeting.

What I'm going to be presenting today in comments was actually presented yesterday in a portion of my comments for those of you that were on the SAP

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in talking about what the public, what the public would need to know to be confident in accepting a model that was used for risk assessment and setting policy. And I'll teller it a little bit to this topic but really it applies very close to what we used yesterday, so I'm going to go through it rather quickly, I also know there's some new SAP members here today.

So what would the public need to see to be confident or comfortable with the use of any model and three subject areas, the subjectivity, the uncertainty, and the transparency aspects of every model. Risk assessment is not a science and all risk assessment is quantification of expert judgment and I think that's good, but it should be recognized that their expert judgments that come into play at many, many different stages along the development of a model and the use of that model in development of the risk assessment, thousands of judgments could be embedded within it and those should be named and stated.

Uncertainty, all the decisions are made under uncertainty, it doesn't mean we should delay the

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decisions but it does mean we should have a sense of what the uncertainty is. The uncertainty should have numbers attached to it, we know it's there, how much is there. I would look to see an uncertainty analysis particularly if the sources of data, each source of data that's being used to feed into the model including the modeling predictions, so for example what we talked about today if the drinking water data is coming from a monitoring data for instance from open water sources or from tap water monitoring if it's coming from monitoring data that was taken say three times a month throughout a season or a year or maybe it's only coming from three actual data points, three monitoring points, that's possible, that's been done before, I want to know about it, I want to know if all the monitoring was done in one season or if it was done throughout the season, I want to know if it was done in the season in winter when no pesticides were never being used on the fields for example.

And at some uncertainty analysis of each source of data including these kinds of modeling predictions, the LifeLine Group that presented to you

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gave several examples where they do reveal this in their models at multiple stages, there are other modeling companies and contractors who also have ways of revealing this in their data, some of it I have

seen, it's very easy to click on a point or a data set that's been used to feed into the model and to actually open up a small file that will tell you if that data set comes from 12,000 points of 12 points and when it was collected seasonally or something like that, whatever the parameters is relevant.

A sensitivity analysis should be done to compare the effects of uncertain assumptions and which uncertainties matter the most, and some of that was talked about by the LifeLine Group that presented. There are some ways to know whether you're taking out your high end users or high end eaters or your high end consumers, or high end apple juice drinkers or leaving them in, how it's going to effect the model, I want to know about that, if they're removed I want to know and I want to know what the effect of that is going to be on the model predictions.

I want to know if the distribution of

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probabilities is including just the means, is it including all the high ends or maybe it's only including the top five percent, those will be questions that will be argued about at the policy level but everybody should know what their arguing about, so those should be transparent with analyses to show how important it is and how it's affecting the model output.

Transparency, this I think is the most important and I think that the LifeLine Group addressed this very well in their presentation, we should be aiming for developing the least complicated model possible and integrate the model with the explanation and documentation of the assumptions, and I know that this is possible because I've talked to contractors who develop these models for companies and corporations and they've shown me that this is possible.

The LifeLine model actually I find quite usable and they have not only provided it to me but actually talked me through the as a tutorial, because like any good scientist I never read the manual until

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after I've tried it myself and the manual only becomes something that I use when I get stuck and they have been able to work through that and I've actually run through some for example recently on perchlorate which has been detected, it's a rocket fuel, it's been detected originally first in lettuce and milk and drinking water and I wanted to look that those parameters.

What I found with the LifeLine model is that I could actually put the numbers that I knew from the data perchlorate found in lettuce I could put that on lettuce or I could actually break it out, I could put it on red lettuce and head lettuce and on kale or all of that, so that kind of transparency was very easy with a click of the button with model and it was

helpful for me when those models are being used to know what kind of decisions are being made and what's being left out.

And explicit uncertainty analysis can help to decide how simple to make the model and obviously we think the simpler the model the better, in fact there should be a rationale for choosing one data set over

another and for how many data sets are going to feed into the model and for some kind of rationale to describe your confidence level in each data set that are going into the model and that would contribute to an uncertainty analysis as well.

Einstein said a theory should be as simple as possible but no simpler and I would add if it gets much more complicated than that people should be asking questions about why. So what we recommend is that the Scientific Advisory Panel recognize that all models that are going to be used by the Agency included a built-in list of assumptions, the LifeLine people gave you examples of a number of assumptions, I could give you other examples and I know that you could provide many more, but the sensitive subpopulations are the most obvious age distributions, full age distributions are another obvious one, and then assumptions about high end users or high end eaters as an example seasonal distributions.

Those should be stated and any assumptions that are made that are built into the model should be stated and quantitative estimates of uncertainty

should be provided and a sensitivity analysis. And then if these are provided that could be used to try and advise the Agency on the use of any uncertainty factors that should be applied to any policy decisions coming out of those models generated relying on those models or of those can't be provided by modelers then the Agency should be rejecting the use of that model because it's not a transparent model. Thank you very much.

DR. HEERINGA: Thank you Dr. Sass. Any questions or clarification?

DR. PORTIER: This is Ken Portier, there's always a danger in showing me the same thing twice because I get to think about it in between.

You use the phrase quantifying confidence in the data sets and I was thinking about that, I have seen qualifying data sets where you kind of look at the lab, you look that the researcher's record, you kind of come to a decision whether this person is producing good data in general.

I can take a data set and assess it against a model and see whether there's confidence in the data

kind of following what is a generally believed model but I don't know how had quantify the quality of a data set outside of the model, do you have any ideas

on that?
DR. SASS: I do and just to prove to you how naive that I am I will tell you that these are not my ideas actually, some of those points come from Max Henrion (ph) who works for a company that designs models for corporations for pay, for a profit company, and his suggestion is that you actually consult people in the field who work with those kinds of data sets to advise you, so for instance if it was a water monitoring data set and there are people that would be able to tell you and really I'm going to give you a simple example, I know that if the data on pesticides are collected in the winter that's -- I don't have a lot of confidence in that data set, those kind of questions, if the was collected in still water versus running water, it it's collected in urban water versus rural water, if it's collected before or after a rain, he actually has that data built into his data sets and with the click of a button you can actually see that

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on the data set including how many points are connected.
So his suggestion is you talk with experts in the field that the Scientific Advisory Panel could probably advise on those things, but that's what I was thinking, those kinds of things.
DR. MACDONALD: Just trying to clarify what you meant by the public wants to see subjectivity, I think what you mean is that they want to be aware of the subjective elements in the model, that's going to take an awful lot of education.
DR. SASS: Well you see the audience is filled with public interest people here and they're all willing to learn. Yes, I'll work on that part if you guys work on providing the information, how's that?
DR. HEERINGA: Thank you very much, Dr. Sass, the presentation. The second scheduled public comment is by the Carbamate Working Group Task Force and we have two representatives today, Ian Kelly and Muhilan Pandian. You can introduce yourselves individually.
MR. KELLY: I am Ian Kelly from Bayer

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CropScience and I'm here today representing the carbamate working group and will be followed by Muhilan Pandian from Infoscientific. While the slides are up I can go through the introductory one. The carbamate working group is an industry task force and we have formed to address the science issues arising from conducting a carbamate cumulative assessment.
The member companies that are three are Dupont Crop Protection, Bayer CropScience, and FMC Corporation. And we cover the majority of the compounds that are in the cumulative group that Mr. Miller talked about earlier. If we could have the next slide please and the next slide.
From the CWG perspective we are really

excited by the steps that the Agency is taking here, we are very encouraged and supportive of EPA's state of intention to use publicly available exposure models that can import data in a standardized format and can create output files based on defying data structures for subsequent analyses using the PBPK models.

And we also, I think the first step to that in having the LifeLine Group task to develop a white

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paper detailing a genetic approach to deliver appropriate exposure metrics from existing models to the developed PBPK/PD models for the N-methyl carbamate group of pesticides is a really excellent first step to start considering what the issues are.

I think one of our concerns from the white paper is though how it went quickly from being genetic into where it talked about modifying the current LifeLine model, and I think there are some issues there that we would like to discuss and I think one of the things that can happen here as soon as you start modifying the model without a full detail of the data structure I think you quickly get into decision points that unmake assessments that will drive the outputs there that may not be the best overall so you shouldn't -- I think you can potentially limit future developments and overlook alternative solutions .

And EPA from the paper that was put out they're currently using three publicly available models, they are LifeLine, also CARES which is from the International Life Science Institute, another not-for-profit organization that has control of that

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model, and the DEEM Calendex one from Exponent (ph), and I think these models were all developed when we started to get into really the aggregate and cumulative assessment as we've got today, and I think lot has been done by the Agency over the last few years in comparing these, trying to look that them to quality assure one against the other to a large extent, and I think that we found that some models do some things very well, others do others very well, and that were developed to some extent in isolation, I think we have learned a lot from that process and I would hope that when we moved into this process of taking the next step in risk assessment that we looked at these holistically as we were developing these and that we really look seriously at the data structures, what each model could do or each model couldn't do, and make sure that we're developing models that answer holistically the question and also give the public confidence that make doing things in different manners that we are coming up with a similar result hopefully or at least isolating the areas where there are for future research, so would like to make a plea that

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these things are looked at together these models to make sure that we get the best output.

I think one of the things that just as an example and we have put in some written comments as well on some areas that we think are limiting to some extent and we have heard the panel talk quite a bit about the 10 minute interval and it creates large data files and it may exceed the capability of the hardware, it may be inappropriate for some assessments and Dr. Price has talked about these issues as well, but I think that there are a lot of ways when you look at the models available that you may want to resolve these problems and you may want to resolve them differently depending on the architecture of the model, and I think it is really important that we do look that these things together and not stop developing one model and then come along and find that we cant compare and contrast effectively, so we would like to see alternative approaches explored for specifying timesteps and various other issues within the -- if you look at core currents and how these are handled.

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From a CWG perspective the Agency had indicated that they were going to be moving in this direction and we have started some of the things that we feel need to be done there because we know that ideally you would want more time to do this, and we are under clearly quite considerable time pressures given where the FQPA mandates are from preliminary CWG work has identified several areas of data management analysis that require careful consideration to insure that all available models can import comparable data and generate relevant output and can be used for the model and I would like to hand over to Mulihan Pandian from InfoScientific to talk some more about these efforts and what he's been doing.

DR. PANDIAN: My name is Muhilan Pandian and I'm with InfoScientific and we are assisting the with carbamate working group with their efforts and developing a cumulative assessment. Before I start please allow me to thank EPA and this panel to provide the opportunity to give comments here related to this SAP issue.

The flow of my comments is based on three

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factors, first I will briefly touch upon some PBPK related issues and then move onto exposure related issues and then talk about what the CWG, the carbamate working group has been doing in some of our efforts.

I have been working with exposure models and post exposure modeling and related software development that for the last 15 years. In some sense if you work with these things before there are natural connections that happen between these, and I don't call these models anymore, these are typically modules, we are in a computer age where we are object oriented, they're much more advanced where connecting should not be an issue at all, we are talking about

things naturally outputting something from a module should be automatically inputted into another module.

There are a lot of way to do this automatically through the software and that's the reason I listed this PBPK list of inputs. If you look at all the inputs of PBPK module would require it's chemical exposures obviously you want them to do route specific, dermal inhalation and oral. In the case of oral it could be resolved even further, is it coming

from food or hand to mouth exposure and the organs that you're considering in your PBPK. If you look at literature typically you will see multiple versions of PBPK models, they are specifically connected to chemicals, for this chemical here's a PBPK model, for chemical two another PBPK model, mathematically speaking software development advice you can envision one PBPK model that accommodates a lot of the organs that you should be able to turn off or on depending upon the chemical of interest, that's how a software development person would look at it. And that kind of a consideration has to come into your PBPK developing process.

Once those organs are considered obviously you need additional inputs of organ volumes, blood flows, and dynamics that happen internally within some of these organs. The initial consideration is elaboration on your alveloar inhalation. Once you have your inputs and your models these are the outputs you're looking for in your PBPK module, chemical concentrations at least at these levels, organs, blood components, expired air and excreted material, urine,

feces, and in the case of the carbamate you're interested in cholinesterase activity, so depending upon your chemical interest you should be able to turn on or off certain parameters. In your case in our example as I will go through in a later slide you looked at cholinesterase activity.

And you have talked about this interface exposure model output and PBPK model input, seamless connections and so forth, and I think what's been put on the table here based on the LifeLine Group's effort they're calling these two separate models, okay take that out, add it to the PBPK people and to me it's more having it in your computer and you could have those as two separate models or in a certain software engine where both are deciding, you run one, look at the outputs and the file types automatically recognized by the next and automatically you run the next PBPK model there.

And here's an example off a model output from an exposure model. I have two tables here, table 1, I will briefly walk through some of the components there. If you look at it column wise id's what I'm

assigning to a person, so take a person and day,

what's that day that you're interested, here I've given an example of day 33 in a 365 day period, in time and specifically I did not identify units and this was also talked about the amongst the panel members you should not restrict yourself, you should be dynamic say in one example you put 15 minutes and 60 minutes, if it's hours it could be one hour, five hours, and so forth and the chemical of interest here I'm specifying as example cast number dermal exposure, inhalation and oral in milligrams and oral again you can dissolve it into food and hand to mouth, so this is one of the tables you're looking at.

And the second table is associated with those people with whose id's are there they want to know what gender, age, height and weight, this allows us to generate all the parameters that the LifeLine Group talked about for example on a software like P3M, so basically these are the two tables you're looking at generating.

One of our recommendations is at this time it would be with worthwhile for EPA to think about a

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generic PBPK model to be identified here is some exposure models and these are the requirements of PBPK models. Come up with the data structure, come up with the list and say hey, this is what exposure models should be spitting out for PBPK models to pick them up, and then a bunch of exposure models can look at that and say hey that's great and we have a lot of work in that round and nothing should be restricted, but here instead of just focusing on a single scenario, single model that was talked about here, so that's what I've have listed here, height (inaudible) of PBPK inputs, that should be an exercise, okay, these area all inputs that I needed for the PBPK models that are out there, consideration of multiple organs, is it three organs, five organs, ten organs, height (inaudible) of outputs.

Once these specifications are made then more than one software development group can go ahead and satisfy those needs. And the last two points, development of data structures based if they indicate in current days based on software issues you can say have it in Oracle, have it in Access, have it in

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(inaudible) these things help software developers to build seamless less models and software development issues itself and I've said this so many times myself and some of you may have heard this and it may be new to a lot of others here, the software field is so advanced that our scientific community has not embraced it at all and we start talking about restrictions because the software development process has been limited, we haven't advanced ourselves enough to take advantage of everything that is out there, so we should not restrict our scientific advancement because we have not included a lot of these features

into the software development process.
As part of the carbamate working group and CARES we've advanced CARES quite a bit and let me start by saying some of the previous persons indicated that there are no cumulative assessment models out there, CARES has quite a few models inside of it to do cumulative assessment on the residential side, on the dietary side, as well as on the drinking water side, you can conduct a cumulative assessment providing multiple chemical information, so I want to make sure

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that's noted in the record.
And the first bullet there, as part of the carbamate's working group effort what we did was we took the CSFII data that's the starting point for EPA's full consumption summary, we reanalyzed it based on the recipes that they have and generate a minute-by-minute consumption data file. And we have a model inside CARES that can handle a cumulative dietary assessment that was used for the carbamates working group.
And this model accommodates co-occurring residue samples and the LifeLine Group mentioned that they combine these right now and there needs to be a policy set or some effort put forth to continue programming but we have that right now in CARES. This model is a CARES compatible model so you will not see it in the public portion, but as part of the carbamate working group this is some that they've advanced.
And the last thing is what this allows us to do is allows us to determine contribution by food and by chemical which wasn't possible previously. And PBPK model and CARES, inside CARES there is the CARES

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compatible model that's PBPK and also a separate model that's PB model that they're currently testing as part of the effort with the carbamates working group, so we take the cumulative dietary model that I mentioned in the previous slide, generate outputs and we push those outputs through this PBPK model which is a CARES compatible model that's currently existing.
And this model will hopefully be made available to the public in the future once the carbamate working group has worked through it and made a presentation to EPA. And here's the example of what we have and actually this model if you open it inside a software engine this is exactly how it will look. If you look at the components we've taken advantage of some of the graphical object oriented technology, you see all those little dots there, I don't know if you can see all the colors, the green colors are the inputs, basically dermal inhalation and injection, and the light blue are all the excretion parameters, so you can go in, click on those, open those, and provide inputs and look at outputs after making a model run. So it's a very dynamic object oriented environment

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that they have implemented here.
And in conclusion I would like to mention in this whole process of advancing going from aggregated cumulative and then onto PBPK/PD no restrictions are made, this is the time and we're trying to design new models, advancements in software, this is a time to not limit ourselves and make transfer and default assumptions and make sure our development is not independent of existing exposure models, it's good to consider everything that is available out there.
And finally, make it a fair and open participation process of all interested stay colors. Thank you.
DR. HEERINGA: Thank very much, Dr. Pandian. Are there any questions or clarification for Dr. Pandian from the panel?
DR. LU: Could you summarize the difference the model you have versus the model presented by the LLG by just maybe one paragraph.
DR. PANDIAN: I may not be the best person to summarize it because I have not used the LLG's model, I have just read their documentation, but one thing I

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can say based on what they mention in general about other models they indicated that there are not cumulative models out there, I would correct that and indicate CARES as a cumulative assessment model which means it accommodates multiple chemicals and terms of outputs we generate so much output. This is one (inaudible) I can safely say and I would look the LLG group to correct me if I'm wrong, the way we build a model is by connecting different models, for dermal inhalation, injection, population, injection, these are all tiny models in an object oriented fashion, at any model stage you can right click open, look at what the impact files are, look at what the output files are, it's very transparent, anything that's in the backbone it's all visible, all the data files are visible, you can export them, you can play with them on their own, and I believe you cannot do that with some of the other tools, there's a very nice tracking system there. And we do not limit ourselves in expanding it, our architecture allows us to add models rapidly because they're all different models, so we do not build an environment which has to be re-coded to

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add additional models because we work on a system of input and output.
If you're familiar with -- there's a name for that start program in the Mac environment, it's a simulation package, (inaudible) program, it's a simulation package where you can connect models, provide inputs and outputs, that's how we built our system.
DR. MACINTOSH: I was interested in the comment that you made about how these models aren't fully utilizing the capabilities of software currently

and I think you mention a couple maybe in terms of the variable timestep and maybe in the visual interface with the object oriented programming.

What are some other areas that you think are under utilized?

DR. PANDIAN: Speed is definitely the issue and in today's environment we should not be running these models from computers, they should all be internet based, that's a clear example, so you take advantage of three or four parallel processing computers that are out there and the user will be

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running a model in his or her computer not realizing it doesn't even reside in his or her computer, it's elsewhere and they just have to look at it.

These are all directions that we should be talking about, maybe talk about data structures, PBPK model and so forth and I don't see those kinds of discussion, it's all based on one or two models that are out there and advancing them whereas I would like to see us jump a little bit ahead of that, hey, here are all the tools, let's how we can take advantage of that, that's just one example, Dave.

DR. HEERINGA: Thank you very much.

DR. PORTIER: I want to be fair to LifeLine Group in that when I look at what comes out of the LifeLine model in the sense of the table 2, table 3 that we're going to be talking about I see that as the data for an individual object that I could pass to your PBPK model without having to run it through CARES, I mean CARES is just another way of packaging in my mind the information that have on activities, diet, residue, to come up with an exposure data element for each individual, so LifeLine's got one

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model, CARES's got one model, DEEMS is another model, the panel has looked at these models a number of times, and I agree with you that I'm interested in seeing PBPK models, but if you've got any ideas of information other than what the LifeLine model is putting into those tables I would like to see it because I think that is going to be one of the key things we're going to talk about this afternoon.

DR. PANDIAN: I fully agree with your comment. My comment related to that is don't look at LifeLine, don't look at CARES, don't look at DEEMS, come up with the data structure, input structure that an advanced PBPK model can accommodate and then tell the expert modeling people, hey you guys meet this need.

DR. PORTIER: I think that's what's already happened in terms of a lot of the discussion we've had on exposure modeling in the sense that all of these models start with the same data inputs, they start with the NHANES data and the CFSII data and (inaudible) data, the only data we have available and you're all working from the same input data, they have

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different core processors and they're going to produce to same output structure, the internal models are transparent in all cases as far as I'm concerned, so that I don't really see that it's that critical, you're all starting with roughly the same data, the model is a conjectured structure that different groups have in how they put it all together, we're going to come to this output exposure data format that we're going to talk about today and then that's going to fed into a CSFII -- I mean a PBPK/PD model on the other end that's going to process it and we've got a lot more discussion about what's going to come out of that model for risk assessment as well, so I really don't see this as -- the white paper as a big problem or that the white paper is specifically tied to LifeLine, LifeLine in my mind is one of the approaches to integration.

DR. SOHN: I wasn't going to say anything until you repeated your point twice. Generic PBPK models tend to become the do all PBPK model in the sense that data structure in fact imposes you to operate in a particular manner because of the

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complexity of ultimately your input files, so actually I disagree with the idea that we should have the generic PBPK models, we should have perhaps readers that transform information from exposure to PBPK models appropriate for the type of PBPK model that's being used, but let the PBPK drive how the information has to be passed and in fact discryptize as a function of time or is actually very opposite to what I think ought to done, it should be flexible to allow you to handle the kind of information that's required for the particular simple for compartment PBPK model or the massive PBPK model that sometimes we're going to be using.

DR. PANDIAN: That's exactly what I had in mind. I may have misstated it. In the PBPK model let's say you have 20 compartments you may just want to run two compartments, your model allow you to run just two compartments based on the inputs that you want to provide there.

DR. SOHN: Well in fact I don't to turn on a model that's 10 gigabytes large just to run two compartments and that's kind of the kind of systems.

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DR. HEERINGA: Academic flexibility I think.

At this point thank you very much, Dr. Pandian, I think that stimulated a very interesting and productive discussion and clearly is relevant to this afternoon's deliberations and also to the report that's being made. Thank you and Mr. Kelly as well.

At this point we're at 12:20 and what I'm going to propose that we do is that we break for 40 minutes lunch, I don't think it is going to be sandwiches I believe, and what I would like to is have

everybody return here for a start at 1 p.m. and so let's plan to reconvene here in this room at 1 p.m. Thank you very much.

(Lunch break.)

A F T E R N O O N S E S S I O N

DR. HEERINGA: Welcome back everyone to the afternoon session, our December 3 meeting of the FIFRA Science Advisory Panel on the topic of the N-methyl Carbamate Cumulative Risk Assessment. As we begin I want to again apologize for having to sort of keep this meeting on pace, I do want to make sure that we

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are able to cover and address all of the questions and the concerns of the panel in the time that we've allotted and while we would in expectation have a full four hours from now or longer in reality we have sort of an attrition process that will begin to occur as we approach in the afternoon. I want to make sure we move into things as quickly as we possibly can.

As a matter of protocol I will ask one more time whether there is anyone who would like to make a public comment to the panel and if so they would be requested to be limited to five minutes, last call then for individuals who might like to make a public comment.

Okay not seeing any let's proceed onto the four charge questions that have been presented by the Health Effects Division and I will turn to Dr. Lowit or to Mr. Miller to read the questions into the record.

MR. MILLER: The LifeLine Group's white paper entitled Designing Exposure Models that Support PBPK/PBPD Models of Cumulative Risk presents an outline of the fundamental procedures and logic

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required to deliver appropriate exposure metrics to the Physiologically-based Pharmacokinetic/Pharmacodynamic model for the N-methyl carbamate group of pesticides. Specifically, the new exposure assessment requires an approach that will modify the exposure information that is currently produced, extend the software to provide additional information on the individuals being modeled, and define the technical process by which information will be transferred from the exposure model to the PBPK/PD model. The LifeLine white paper also discusses the data requirements of a PBPK/PD model, briefly reviews the state of the existing exposure assessment models and their outputs, and presents both a general approach and an N-methyl carbamate-specific approach of how the exposure simulation models can be adapted to meet the needs of a PBPK/PD of cumulative risks.

The question is please comment on the detail and clarity of this document.

DR. HEERINGA: Our lead discussant on this question is Dr. David MacIntosh.

DR. MACINTOSH: So in keeping with past SAP's

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I think what I will do is I will make some opening comments and then I will deliver some specific comments that I have and then turn to the other discussants for this question and their comments.

So to begin with the assessment of cumulative exposure and risk assessment comes with -- the assessment of cumulative exposure and risk for N-methyl carbamates is a challenging task. Personally I would like to recognize the Agency for their ambition and their continued support or pursuit of multichemical issues and the consequent driving force that is created.

Clearly as we've heard this morning and many of the assembled here have worked with in their own careers there are many conceptual and technical challenges that need to be resolved. In the November 8th, 2004 report prepared by the LifeLine Group provides an introduction to many of those issues and to approaches for addressing them as well. And as David read into the record the SAP was asked to comment on the detail and clarity of that document.

In my opinion the report is sufficiently

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detailed and clear for some issues, for other issues however more information and examples would greatly improve the utility of the report for establishing the common foundation for moving forward. I find that the report does a good job of stating the problem, describing the current capabilities of the LifeLine model and proposing conceptional approaches or a person oriented approach to a length exposure in PBPK/PD model.

The report has other favorable features that I choose not to go into at this time in the interest of time and trust that they are either self-evident or can be identified by omissions from comments about areas of improvement that I will make or possibly identified by other panel members.

So there are several areas or topics that I think should be considered for further elaboration in the document, many of those interestingly are topics that are closely related to those identified by the LLG group during their presentation this morning namely timestep, exposure concentrations and this interface between models. For instance, two of the

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most important factors in determining dose to a target tissue are anticipated to be the occurrence of the chemical in an exposure setting and also the absorption and metabolism elimination parameters that represent the steps from exposure to dose. In other words and in my mind that's the beginning of the process what's there, and the end of the process how much at the very end is to that target.

Among those factors I think I find from

experience is that the ones with binary numerical expressions are likely to be very important. At the beginning of the source to tissue dose in the person oriented model or any other model you have to deal with is the chemical there or is it not there, is it used in the residential environment or is it not used, and I'll elaborate on that in a minute. And the back end of the process that is rapidly expanding world of knowledge that we are fortunate to live in we are quickly learning about gene environment interactions that can determine the presence or absence of important phenotype, say some detoxified enzyme that may or may not be present in an individual, and again

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in my experience in doing this type of modeling the presence or absence of such a detoxifying enzyme at the very end of this long calculated long set of calculations can make all the difference in determining whether somebody's at the high end or low end of an exposure distribution. Just like whether they used it or didn't use the chemical at the very beginning, I find that those two pieces are probably the most important.

So I would find that some greatly expanded discussion of those types of issues in the report would make it much more or useful and that's what I find kind of interesting that there's very little discussion of those issues in the report.

So let me elaborate a bit on the front end of the model, the sources. So for a cumulative exposure model to adequately simulate exposure to the N-methyl carbamates the model should include the processes that result in the introduction of those chemicals into residences or any other exposure settings as well as the transport of those chemicals within that exposure setting and possibly out of that exposure setting.

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So knowledge of the products that contain those chemicals is essential because they define the exposure opportunities. And based on the detail that's in the present form of that report we can't be sure that the model is envisioned in that report accommodates all of the carbamates in question. I personally would like to have seen a listing of the products in which these chemicals are registered for use or at least classes of product types, the release types, are they foggers, are they crack and crevice, are they registered for use in lawns, what foods are they registered for use on, some idea of the prevalence of these chemicals, and I don't find it and I think that would be helpful.

And why I think that would be helpful is that it would help the panel or any other reviewer of that document focus on the aspects of the models of these cumulative model framework that might be most important of getting an accurate assessment of exposure, without that they're all equal to me and it

seems unlikely that that's really true.
Likewise knowledge of the physical and
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chemical parameters that influence the transport and fate of these chemicals is also important. This morning we had an opportunity to ask some questions and get some answers about the proposed framework and one of the questions had to do with is the model time dependent, is it truly dynamic or is it intervals of discreet steady state-like operations and the latter was the case. I should have asked then and I will just pose it kind of rhetorically now and if you could answer it it would great, it would seem to me that a model of this type because it's going in timesteps now should account for the movement of a chemical from one place to another or from one medium to another in a given exposure day or setting for a person, and as such there should be a mass balance component to the model, it should be tracking the stuff that's in there, and there's not enough detail in the framework as written for us to determine whether that principle, that mass balance principle is applied.
And turning back to the endpoint of the assessment back in internal dose and delivered dose to some tissue, again the report offers only little
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detail on those issues, and as a physical scientist I'm not really qualified to comment much further on that particular aspect and instead would rely upon my colleagues on the panel to address the topic further.
That said though I have a few more items I would like to identify as they are relevant to the detail and clarity of the report. Excuse me while I look at my notes, some of them I have to skip over because they were discussed this morning. One issue I would like to note and thereby reiterate is this idea of the 10-minute timestep or any discreet timestep, and in particular the allocation of exposure over a 10 minute period or within that 10 minute period and again it can be any interval that we're talking about, I have some reservations that -- my understanding is that exposure in one of those intervals would be allocated as an average over that 10 minutes so as the exposure was really to thought to have occurred over a minute that the quantified exposure for the model for that 10 minute period would be one tenth of the actual experience and maybe I'm wrong, but that's what I understand, and if that's the case then I have some
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reservations about the accuracy and even the validity of that approach.
And if the idea is here and I think it is, obviously it is to get a cumulative dose and the concern for chemicals such as the N-methyl carbamates seems to me to be an acute dose, so that means we want to get the timing right, and if we know from the git-go that the model framework doesn't allow us to

get the timing right it seems like not a good place to start .

Moving to a different topic, I found that the report had and the framework described in the report had a great deal of detail about the dietary pathways relative to other pathways, and I would like to see more detail provided in about the non dietary pathways because I think it would contribute to the clarity of the framework, it is really unclear about what's going to be done with the non dietary exposures.

Looking within the non dietary I would find additional information about the dermal absorption of multiple chemicals with similar structure and activities would also improve the clarity. For

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instance, will the loading affects on absorption rates be considered, typically higher loading on the skin results in a lower rate of absorption of a given chemical across the skin and now we're talking about multiple chemical and they're similar structures and it seems to me that the potential for simultaneous exposures to similar chemicals to influence absorption rate should be considered, but for that matter it's not clear from the report either how absorption will be handled, it kind of alludes to for showers and bathing and concentration of time, but for the other ones it doesn't really spell out what would be done and I think that would be helpful.

I also believe that further description of the inhalation exposure pathway is warranted and I say that in particular with respect to again the timestep nature of this modeling framework. Obviously you're talking about inhalation you're talking about a substance in air, air is incredibly more dynamic medium than say surfaces which longitude and exposure studies many of them show that for pesticides and surfaces concentrations are relatively stable from

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time period to time period across days and even weeks, but air is totally different, totally different, and so that to me seems to be something where we would want to account physically for the movement of a chemical from one space to another over time in an exposure setting and allow for it to leave an indoor area through just ventilation, and also maybe to have the air concentrations tide to the service concentrations which may be the case, tied to it, I mean correlated.

Lastly, I think the clarity of the modeling framework as proposed in that report would also be improved by expanded discussion of absorption distribution, metabolism, and elimination, those processes are mentioned, they're mentioned as being important, yet section 5.E.2 which is entitled Model Time Dependent Physiological Parameters makes no mention of those factors and that surprised me.

So with that long winded comment that concludes

my thoughts and would like to turn it to the discussants.

DR. BRIMIJOIN: This is actually something

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that's very difficult for me to comment on, I guess the question for me of course is always read several ways and the question is really about the adequate detail and clarity. I actually was surprised as how easy it was for somebody coming completely outside the area to get a reasonable sense which I think subsequent amplifications here this morning proved to be correct about which the fundamental way this software is going to work on the issues it's attempting to address, but I actually -- I think at that level I think the document is surprisingly good.

We just heard from someone who is a physical scientist who is hungry for a good deal of additional information which actually if it all were provided might -- I mean if it's provided in the wrong way it will likely decrease the clarity while increasing the detail, but nevertheless so that's one group of users and so who are the unusers of this white paper. And I guess it does have to satisfy at least two constituents, it does have to satisfy toxicologists who are going to be asking questions when this public domain software comes available, can I use it, do I

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know what it will do, and I think it comes close to that, but for the purposes of the let's say less sophisticated users I think it can go a little bit further, I notice in the oral presentations today by Dr. Chaisson especially there were a number of additional slides that were not incorporated into this document, but mostly in the form of examples, examples are very helpful in proving a person's general understanding of what's happening, it's much less abstract and I particularly like the pictures of the children in the living room and stuff like that, but I think that document could benefit by having some of these additional visual aid from that standpoint.

On the other end on the more sophisticated end I am at least able to comment I guess I see -- I myself was grappling with the fuzzy outer boundaries here which my colleague Dr. MacIntosh has really dived into in detail. It seems to me that the fundamental task you're trying to do here is model exposure, and we keep coming back to that, it's modeling exposure, we're going to let the PBPK folks dialogue with them and figure out what sort of metrics they need at the

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input into their models and then we're going to do our best to construct a seamless interface, and that all seems all pretty clean until we get to the issue of well should the guys that are modeling the exposure also be tackling the issues of all these highly variable physiological parameters and vary on a daily basis or actually a minute-to-minute basis, as fine a

timestep as you want about cardiac output and flow different organs.

And so listening to that suddenly my concept of where the environment ended and the organism began started to get stretched and it became very porous and I think that the way I see it is again you're basic goal is really to model the delivery of compound to a potential site of intake, that's your basic goal, and then the nature of the engine that you're developing is such that in fact you are able or would be able before we cross the boundary into the PBPK differential equations you're able to model more precisely now the delivery to very specific sites actually inside the organism, so now we'll be modeling what might be coming into a well perfused organ or a

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poorly perfused organ, and that's where there was a call for much, much more information and much, much more consideration of the dynamics that is coming from Dr. MacIntosh and it's fair, and so if you're going to take that job on I guess you got to be prepared for that level of demand from your consuming audience here, but as I understand it that is somewhat of an option as to how far you would go with it and really even almost at the discretion of the user which kind of PBPK model they're going to take, whether they want to handle all those aspects themselves in their model with it's perhaps less limited data handling capability at more sophisticated dynamic equations.

So those my general comments and you can respond as you like, but on very, very small level I would say that there is small things you can do to the document that would help at least some people, it's quite well written although it does need more proofreading I have to say, but one thing I think I would really like to see you've got a nice list of definitions of terms, it would be a very helpful if you had also somewhere, front or back, a list of all

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abbreviations you have acronym soup in here for example CFSII is never defined, I know what it is, but there will be people who want to read this document who don't, I suggest will turn it over to the next character.

DR. FREEMAN: I would like to congratulate you on the development of this white paper, I think it's a very interesting overview not only of the history of the exposure risk modeling and the Agency but also its description of a very ambitious plan that's going to make major change in how exposure risk modeling are conducted in the future.

I think earlier Dr. Lowit discussed some of the many activities that the Agency is doing and they're alluded to in the introduction to your white paper and I haven't decided whether that should be expanded so that people can understand how all of this is going to come together, you're going from using

index pesticides to multiple pesticides, you're going from doing sort of long-term temporal units to short-term or at least to have the option of having variable temporal terms in your models, and you're

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incorporating lots of stuff in terms of physiological parameters from the PBPK modeling, and it's a huge and ambitious program, and I look very much forward to seeing how it actually works when you get to start tinkering with it.

There appears to be several limiting factors some of which may be specific when you're using the carbamates as your example and a lot of these have already been discussed. One is this using the 10 minutes steps, another is the ability of the PBPK models to absorb the data from the exposure models in the seamless fashion, and also the depth and breath of data that's available on specific subpopulations. For the most part I don't think any of these limits are insurmountable. The focus on using the smallest timestep that is manageable seems to me to be less interesting than asking what is the smallest or largest timestep that is needed and why is it needed.

In reading through it sometimes it seems to be driven by what's needed for the PBPK model, other times it was less clear that that what was going to drive your using your 10 minute step. When you set up

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a timestep I guess what I was interested in finding out is how would you go about testing the adequacy of the time period that you have selected. You know if you use 10 minutes rather than 15 or 20 minutes or an hour does it really make that much difference in the long run, and to some extent that depends on the chemical you're looking at, but beyond chemical dependent needs are there other things that will influence it, and I wasn't sure how that went.

The major concern reading the document is the issue of how to seamlessly go from the LifeLine exposure assessment or whatever other model would be used to the pharmacokinetic models. I guess one of the things I wanted to know how was is the seamlessness going to be evaluated. On page 42 to 45 there was a brief discussion of kinetic metabolic and capacity parameters and the authors say that these parameters vary across individuals as a function of age, gender, and genetic variation and race ethnicity and I was wondering whether there was enough data particularly on the genetic variation race ethnicity issues to be included in the models are all these

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going to be calculated estimates, I wasn't sure on that.

And there was a brief discussion on page 32 the discussion of the use of the model for evaluating new and existing registered products and several scenarios were provided, I thought that was really

interesting and I would hope at some point that that would be flushed out because I think that would be crucial to the utility of these models for the Agency.

DR. KEHRER: Well at this point I think the detail issue of the white paper has been covered from your point of view in excruciating detail, so I don't really have anymore comments on that. As a molecular biologist/toxicologist isn't in this field although I had some concerns with the clarity issue, and this is really just a writing style issue I think. I found that paper to be written really targeted at a professional audience in your field and that the acronym issue was already brought up, it made it very hard for me to read, I found a lot of jargon in the paper as well and it just seemed like a lot of the sentences were written in convoluted fashion where you

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use three words where one might have done just as well, and so I would just encourage you to think about the audience that this paper is going to be targeted at and any revision that might be done.

DR. WHEELER: Coming from a field very far away from this I think I share those sentiments that it was difficult to read not necessarily because of the material, but just had to wade through the jargon and the acronyms and such, but I do think that it's a relatively clear in outlining at least the ambitious strategy to develop the cumulative risk assessment approach and then link that or at least set up to link to the pharmacokinetic models.

The thing that I saw as a weakness was exactly how that link was going to be made. Spell it out for someone who is relatively uneducated in the field and it may be apparent to people who do this and I don't know, maybe we'll hear their side of it, but for someone who is relatively on the outside of this field that connection or that linkage was apparent. The other thing -- and then there were things that were unaddressed that I think would be important to

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see in the document.

And one of those is -- and we've already talk about it to some degree this morning, was the idea that you're taking data and I think Dr. Portier brought this up right before lunch -- is the idea that you're taking data that everyone has access to, you're assimilating it through sophisticated approach, mathematical approach that you have programmed, and then the output is going to be very similar to what other groups are trying to do to feed into other models, and so what doesn't come clear out this document is what is the superiority in your approach, why is it different, and why is it going to be more useful than what we have other than I understand the value of adding more time points and breaking it down to smaller groups, but really what is that going to allow us to then be able to do, and I think maybe the

thing that didn't come out to me in the document that did come out was the accessibility of the raw data, and I think that is a valuable point that needs to be apparent in the document.

Then I think the other things that weren't

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addressed and I think should be, I can't remember who said this maybe Dr. Brimijoin, the power of informatics, if you're going to go in this field and you're going to make the case that you know you're informatics then how broad do you expect to be and what can you take on, for example are you going to be able to at some point link what you've done with the huge amount of genetic informatics and today that might not be a very important thing or maybe even look way off in the future but I think that day is actually closer than we can imagine, and I think that's a very -- you know ten years ago no one would have thought that we had the genetic information that we do, so I think that's a realistic thing to consider now is are we going to be able to take a risk assessment exposure data and then link that to genetics.

And then I think, the last thing is that underrepresentation of subpopulations, diseased patients, elderly and going back to diseased patients is for example a non-obese so you wouldn't get that information -- so none of these fatty liver for example, the patient wouldn't stand out as an outlier

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because they're not significantly overweight, their eating habits may not be that different but somehow they've develop a fat liver which is going to affect metabolism, it's going to affect organ profusion in the liver and that's going to influence lots of other parameters as well, and I think those are very important questions that need to be thawed out.

DR. HEERINGA: Thank you Dr. Wheeler. I want to look to the other members of the panel to see if anyone has comments specific to question one on the white paper developed by the LifeLine Group.

DR. CHAMBERS: I have a little bit of a concern about one of the things that Dr. MacIntosh just mentioned, maybe I misunderstood it, if you're suggesting that the fate and transport model being included in this I think that's making it too complex, if you're talking about just adding a little text into that document to say whether some of those factors are important that's one thing, but is almost sounded like you were saying fate and transport ought to be included in this exposure assessment and I would tend to think that would be too complicated to be

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manageable.

DR. MACINTOSH: In fact I was suggesting both it be noted, it be described some in the document and that at least be considered for implementation into the model. The notion here is to get it right and to

do it realistically, which actually begs a question in my mind that I had earlier today, what really is the purpose of this model, is it for OPP to use in establishing tolerances and if so -- if that's the sole use and if so how should the model be geared so-to-speak, should it be geared to be conservative, that is unlikely to underestimate because we're trying to protect or should it really be geared towards the best estimate we could get which is kind of the nature of regression equations that we have heard or is being proposed to go into it, that's just a of thought question.

DR. CHAMBERS: I think we all want the most accurate assessment possible but we also have to have something practical and if you consider the types of numbers that Dr. Portier suggested right before lunch the sounds like the data base and the magnitude is

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pretty ominous right now and I just want to raise the question of whether that suggestion is even practical and leave that in the record.

DR. CORCORAN: I'm not certain if my question is best residing with question number 1, when they include a word like detail it kind of opens all flood gates it seems, so please forgive me if it doesn't belong with this question and if you would like to defer to a later point let me know, but this goes to all of the model authors and whoever wants to answer is fine with me.

There is a couple -- there is two considerations and let me begin with one which I think you have alluded to late in the document which Dr. Freeman brought up and that's pharmacogenetics and also Dr. MacIntosh in his comments about the importance of genotype and metabolic phenotype, there's a comment somewhere around page 47, 46, I believe which indicates a hope of future capability of being able to take into account pharmacogenetic variability through the parameters on which the model is currently based which are largely anthropomorphic

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and projections of blood flow, but for many circumstances in which xenobiotic are metabolized flow is not a factor, they are not flow limited in their disposition, so blood flow under those circumstances really becomes a much less sensitive parameter in establishing the outcomes that you generate.

Secondly, the ability to use gender, age, weight, and other factors to capture pharmacogenetic variation is I believe unrealistic and I don't believe it can happen in any meaningful way, so I would suggest for consideration either those comments be removed from the next version of this report or this white paper or a modification be introduced indicating that we acknowledge these are important factors but they would have to be cap tured in the PBPK end of the modeling where I think a significant portion of this

variation has a possibility of being captured, but I don't know if the most important part of that variation can be captured on that end and it is a major concern.

And a second element separate but related to pharmacogenetics is the notion which permeates this

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report as well as the competing approaches used by the Agency in which they use a relative -- and I don't know if I have the right term here -- relative potency factor to a reference agent there is the implicit assumption that interactions will be additive and we all know that in many instances there is competition, there is subadditive, there is synergy where there are directly superadditive or there are unanticipated interactions where for example you may be even changing the synthesis of a target for example over time and it wouldn't be determined through the straight mathematical deduction of additive superadditive competitive interactions, so I believe this is clearly something that would belong in the PBPK model, but I think as one is reading this white paper the notion comes up that well there seems to be possibly an oversimplication of consideration, so perhaps acknowledging that consideration and passing the ball so-to-speak to the next set of modeling attempts and the receiving end might be adequate.

DR. HEERINGA: At this point I would like in an interest of time to move to question 2 with the

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acknowledge of if there's something pressing we hopefully have time to return after we're through the four questions, but unless I see is there an important question -- all of them are important of course, but from the panel on this particular topic.

Let's move onto question 2 and Mr. Miller or Dr. Lowit.

DR. LOWIT: A central tenent underlying aggregate and cumulative risk assessment is that exposure occurs to a hypothetical individual whose specific demographic characteristics such as age group, region of residence, race/ethnicity, sex, et cetera, help define exposure scenarios. The exposure pattern and other data concerning this individual should be kept consistent with those characteristics.

The use of PBPK/PD models in cumulative assessments adds another layer to this complexity of generating and maintaining a set of internally consistent individuals comprising a hypothetical population. In defining individuals for use in PBPK/PD models, it is necessary to maintain logical consistency and linkage between the various anatomical

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and physiological parameters that describe that individual. For example, given a bodyweight, age, and sex of an individual from a reference population such as LifeLine's Natality data set, it iis necessary that

the organ sizes, compartmental flood flows, breathing rates, et cetera, all be consistent.

A recent article by Paul Price et al. 2003 appearing in Critical Reviews in toxicology summarizes much of the literature in this area. The article presents a number of regression and other equations which can be used to generate the linked anatomic and physiological characteristics of those individuals.

There are three parts, part A, please comment on the degree to which the article comprehensively summarizes the available literature concerning the anatomical and physiologic relationships that exist between organ sizes and volumes, blood and other flows, breathing rates, et cetera.

Part B, are there additional data or data sources for these relationships that would be useful to include or consider.

And part C, please comment on algorithms

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provided and their potential utility in use by PBPK/PD.

DR. HEERINGA: Thank you very much, Dr. Lowit. And Dr. Hattis has been nominated to be the lead discussant for this particular response.

DR. HATTIS: I'm going to be pretty quick about responding to A and B because I think the major meat of the discussion will come in C. And the short answers to A and B is that I don't know of major things that have been left out is particularly interest I think in focusing on key parameters like autopocity (ph) and the autopocity relationships where there may be other data in the literature and I know that the group actively investigating that type of parameter.

I have a paper that did some estimates of autopocity in children that can be used for some comparisons, there may be other worth it, but I have not tried to do a comprehensive literature search to locate additional papers, the group in response to the questions mentioned the new NHANES four data that I think are a good starting point for additional

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comparison with the existing model frameworks and would also give you the opportunity to assess whether there are any secular changes in the relationship, at least the basic underlying height and weight types of variables that are the starting points for the analysis.

That NHANES four data may also be a good starting point for adding some stochastically in terms of both variability and uncertain analysis to the existing framework, and we'll talk about that a little bit more later as we get into Dr. MacDonald's comments who needed to leave.

My basic comment is the modelers for the P3M LifeLine system have a sound general approach and reasonable plants for enhancing the system to meet the

future needs for PBPK/PD modelers.
The model framework is deliberately designed to be highly flexible in its outputs in terms of the timesteps and the exposure, roots, chemicals, age groups and other demographic characteristics, organs covered in the PBPK modeling exposure periods and other parameters. Efforts are to be encouraged to

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continue a test and refine the models for different organ sizes, organ blood flow rates, alveloar ventilation and cardiac output against newly emerging data sets including the new NHANES four data mentioned in the question period.
Such comparisons for the external date will be helpful as I said in adding the stochastic elements in the model to represent variability of the estimated parameters about the mean values predicted from the NHANES individual records from the individual characteristics so essentially you're getting a mean expected output but there's residual variability that's not captured in the individual and with that is complicated because the residual variability includes two elements, one, additional real variability from person-to-person that hasn't been fully captured in the height and weight relationships, they're there, but also there's experimental measurements there and that doesn't belong in the variability analysis, so that's a bit of a challenge to deal with that.
You know that the real variability is likely to be bigger than you think but how much bigger is a

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nice question that few people have tried to address, and so I think that's a matter to be thought about, maybe you can you know include the whole extra variability as one bound, but again there's other complications such as the unrepresentativeness of the likely people included in the studies used to generate the equations as been mentioned earlier, and so doing a proper -- doing a full uncertain and doing a reasonably and full uncertain analysis is not easy, but you need to do the best you can you know considering different kinds of possibilities focusing I think on the kinds of variables that are most likely to be influential in the PBPK model.
So as it happens most of the time most of these parameters of organ sizes and blood flow don't matter that much in the PBPK model, what matters sometimes is the size of the fat compartment, to some extent some times for some chemicals the liver flow rate, and sometimes the blood flow to fat rate, rate of flow of blood to fat, fat profusion, right, but once enthusiasm for comprehensive uncertainty analysis of all of these parameters may be tempered a bit by

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the observation that what really matters most often to the outcome and performance of the PBPK models is in fact the parameters that are used to calibrate the

clearance rates, and those are going to be specific to each individual chemical within the content, and those are most likely the things that are outside the current LifeLine projection that -- and so in allocating your overall efforts at understanding the carbamates you're going to need it allocate a fair amount of effort to understanding those, and that's also where all the genetic variability that you mentioned earlier also factors in.

The current model commendably provides for activity related changes and breathing rates and blood flows in the light of changes in activity during the day. One similar issue that has seldom been dealt by PBPK modelers but which is potentially available in a proposed LifeLine system for particularly ambitious modelers are the effects of meals on the tissue of blood partition coefficients. I know tissue blood partition coefficients aren't in your thing but you could at least tell the modeler if he wants to take it

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into consideration that this individual is now 15 minutes, 30 minutes, two hours after eating a high fat meal okay, because you have, uniquely your system has the dietary information in there that would allow you to do that.

What it does in the model is that when you eat the high fat meal essentially you get more lipid in your blood and that can change the tissue blood partition coefficients in predictable ways, so that essentially you get greater extraction of the fat soluble chemicals both from the GI tract but also from the fat stores after you got that, and those differences can be of the order of 50 percent or stuff if I'm remembering the data correctly, you know about that, and so that can make a bit of a difference.

Again, this is kind of a nice to have add on it's not essential, but as long as you're changing one kind of parameter you can at least have the capability for the user of the system to become aware of the timing of the high fat meals.

Peter MacDonald before he left, left the comment on this question that he notes that the

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equations in the predictions of blood flows and breathing rates and organ sizes are deterministic and this goes to the point that I made earlier essentially that this means that all the variability comes from the sampling of the variability that's inherent in the NHANES three data set and there is an addition to some other variability that eventually you might want to put in the model focusing I think on key determined so that PBPK behavior and such things -- such parameters as fat content I think it would be a good choice for a test analysis of the additional variability that you might want to build into the system because of the fact that you're only getting the central estimate of the person specific values. And I'll turn it over to

the rest of the folks.
DR. REED: I have nothing to add. I don't know how the P3M data compared to the physiological parameters used by other modelers in doing PBPK modeling, but I think a common set of physiologic practice is very useful and I really appreciate the effort come up with a set.
My comment is specific to the parameter for

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inhalation rates. The computation equation following Latent's equation based on the ratio of total energy expenditure to basic metabolic rate and I notice that the primary use for prior to A the food energy intake to basic metabolic rate ratio is taken from a compacted value for children .5 to 3 years old. The alternative to using the more age specific values would be good. Consideration should also be given to providing breathing rates that may be more appropriate for short-term exposures, that would take into account different human activity levels and it appears that LifeLine has been using that, it's just not in the P3M publication or the publication for the P3M, and so it would be good to include that too.
DR. EDLER: Actually I think it is three comments. The question may not be possible but I think that was said actually, going into all of this literature we had over the 50 years and looking for some parameters you can do that but I'm not so sure if this is really worth doing. You may do it just to get the transparency of all the parameters done, but I think you would also have to write papers if they have

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really good parameter estimates or not, so it will be an issue, so I think simulating of the parameters you take from the literature might be necessary.
A second thought is there has been an EU project called Monte Carlo done by some people in Trinity College in Dublin. They are more interested in exposure modeling, but I think it might be interesting just to look there what has been done, if there's an overlap or what you can take from them or what's the difference from that.
And finally, there was a discussion in the morning of the variation of parameters and some of the variations of the parameters is not so large, in principle I would agree with that, but just the example mentioned by Dale if you take the blood lipid content which might be interesting if you look for the dioxins because they are transported just by these lipids in the blood, they may have actually a high relative variability because they have so low lipid content in the blood so one should be a little bit careful with this variation actually.
And a final point that came just in my mind

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we are always talking about correlations but I think if you talk about correlations you ought to talk about

correlation between two variables. But you have multivariables in there though that could be actually higher the mention of correlations in the whole data set, it might be explored.

DR. CORCORAN: I believe that comments made in the morning were entered into the record, there's not need to reiterate anything that I touched upon earlier. The only comment I would add has to do with a comfort level of where the model is going and there's no question there will be a crew of new information that will make the model stronger, particularly anthropomorphic data gathered by CTM, MRI, in particular of the area of obesity it's already there, there' the NHANES data, and there's going to be more.

It would be comforting to see some sort of perspective road map of when -- I mean you will continue to improve the model probably perhaps at infinitum but you will reach a stage where the improvements will become incremental and it will be

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comforting to see an analysis that will lay out what you would consider to be the major gaps that you would feel would be the highest priority for filling and once those gaps were filled the changes in model predictions would be nominal for the most part, and a version used two years ago analysis used two years later would return approximately the same outcome, that would be my last comment.

DR. HEERINGA: Excellent suggestion.

DR. SOHN: In reference to first the question I think that some of the terms it is necessary to maintain or is necessary to that the organ sizes be consistent, I think you should be cautious about those kinds of terms because it really is, it's necessary that really matters, it really does, so I think that in cases there's that qualifier that whether a particular organ size is so critical that you need to know at the level that for making predictions and I think you should be careful with posing of the question in that way.

In reference to part A and part B I don't have particular specific comments except in part B

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about other available data, I wonder if there exists models that have been developed to analyze some of these studies and the results of these models can be also incorporated. I don't choose to use the term data, them being as data, but at least some type of information that you can gather in reference to comparisons about regression models for example, and whether these mechanistic -- I should probably choose -- mechanistic models could be additional or other type of models that you would consider incorporating to select or predict organs and tissues sizes.

In reference to part C we're moving in a direction where the models are far exceeding the

capability of the available data, it's pretty clear, and so what do we do. We have one of two choices we say we're not going to make a prediction at that kind of level which kind of stops us from advancing and not, and so we are faced with moving forward with some of these more complicated models, making predictions at these kinds of levels, what can we do about it.

My recommendation is that we need to add consciously more transparency for qualifiers into the

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model predictions that you're making whether it's LifeLine or the PBPK parameter generation or the PBPK model. For example, when I look at these regression lines I have no way of judging the quality of these models, I do not have a fit or correlation plot to see whether regression fits and what extremes were and what poor areas of the distribution fails.

And I understand a big portion of that is because you don't have the data and no one is going to give it to you. Well, absence of having that data should be a qualifier to state in the predictions of your model then for example I'm not going to take the quality of this overall regression line without my qualifiers that I have not looked at, the model developer I believe should take -- the developer of the primary estimation model should take ownership of the type of regression line that they're going to use and if it requires you to first say well I took it at this journal paper without anymore analysis that further at least provides that the user uses some idea of what the quality of the model is.

And I think that's also very important

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primarily because a journal paper that derives a regression line provides that regression line to describe how it fits the data, it's not necessarily developed to say that's the relationship for body weight to this organ across the full range, and clearly as you get to any of these qualifiers well the qualifiers could suggest that for this given body weight from the NHANES data set I am on the extremes of this regression line, that's an important qualifier I would like to know and and I understand you press and you click, click, click and you find that, I think it would be even more transparent and more obvious.

And my last point is in cases ideally where you do have data, the data, the raw data, I recommend considering looking at multiparameter or multi indicator regressions, for example if you have a data such that as links to body weight to various organ sizes or various tissue sizes I suspect that by combining that information and doing it, multiparameter regressions will help you get even more consistent person or a body type or so, and that is ideally when you have that kind of present data, but I

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suppose there's at least some of (inaudible)

diagnostic.
And lastly, one point that we touched on earlier is this issue about feedback from the PBPK model. Perhaps ideally if we're in a system and I know right now we're going from LifeLine to PBPK parameter just to generation to PBPK model, I wonder as PBPK model developers use their model and compare it to bio markers or urine you learn more about the particular parameters of the body, that information could be feedback towards LifeLine, and I think that would be a nice addition or at least a nice hook, I don't know if it exists now or not, that might want to be a feature you might want to highlight in the overall plan of how this will look in the future.
DR. FISCHER: I just have one comment to make and I agree with all the other comments of course. I was surprised to read in the report which is a wonderful report and actually now I'm talking about the paper that you produced which is so helpful that there is no or perhaps no adequate data for modeling. A group of tissues for most of which are endocrine

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system tissues and they include the adrenal, sinus, breasts, reproductive organs, parathyroid, pineal gland, pituitary, urogenital organs except for the kidney, other than the kidney, and a favorite of mine is the eyelets langerhans (ph) in the pancreas.
So when you think if you need information about target tissues and you can't get it that this is a pretty formidable group of tissues that needs to be taken care of, so I think the eyelets of langerhans (ph) are interesting because you can look at the volume and blood flow to the pancreas but I think you're not going to find that's the same as the eyelets of langerhans that are secreting insulin and look at them which are all over in discreet areas in the pancreas because the blood supply to those eyelets is not different completely but somewhat different and that to the pancreas and the anatomy of the vascular system in the eyelets is clearly different, so I wish I could sit here and tell you where that information is in the literature, but my guess is at least I know that's true for the eyelets, that there is literature on the blood flows to the eyelets and the anatomy is

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given and the size of the eyelets are given in general so you would be able to know the volume and maybe for many of these other organs if you go into the literature and ferret that out it would I think put fewer important organs on the list of unknowns, so I would encourage that to be done.
DR. HEERINGA: Dr. Fischer, since you've emphasized the pancreas and the eyelets is there sort of an initial paper that we could cite in our report that we get them started along these lines.
DR. FISCHER: I can get it to you.
DR. HEERINGA: At this point we have the

discussants from the scheduled discussants and I would like to open this particular question again to the full panel if there's a point that someone would like to make, we'll have an opportunity later-on for wrap-up if something else comes up.

I'm not seeing any, I think we're on a good schedule I think to be able to provide coverage of all four of these which was my concern and we can come back time permitting I think for more in depth discussion, but let's turn to charge question 3.

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MR. MILLER: Traditional non-cancer probabilistic risk assessment methods perform a direct conversion of exposure into risk by incorporating the PBPK/PD component into risk assessments in order to more appropriately account for temporal and other aspects of toxicity, output from the exposure component of the model must serve as input to the PBPK component. In order for this to occur, a time series of exposure must be developed for each individual considered in the assessment. Each exposure event associated with that individual that occurs during a given timestep must act as a separate input to the PBPK/PK model.

In order for this to occur, data from the USDA's CSFII must be placed into the exposure component of a model in such a way that separates each individual's eating occasions. In addition, data from NHAPS and other data bases will need to be entered in such a way that each event occurring during a given timestep is distinct and separate. Furthermore, the output from this exposure model must appropriately link or interface with a PBPK/PD model. The LLG's

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white paper proposes that LifeLine be modified such the analyst can customize the outputs of the model for the specific PBPK/PD analysis to be run, selecting from among 23 tissues, organs, and compartments listed. The analyst will then define the duration of the timestep used for creating the exposure history and the duration of the exposure history for the basis of the LifeLine exposure analysis metrics and output file. LifeLine output files will be created as Access files consisting of separate records for exposures of each simulated individual within the defined population of the analysis. Each individual's exposure history will be captured in a record that consists of two tables. Examples of data tables/outputs were presented in the LLG's background document.

The two questions are, A, please comment on the format and structure of the MS Access file containing the records for each individual's exposure and anatomical/physiological parameters, tables 2 and 3A of the LifeLine Group white paper.

And B, are there additional parameters or

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options that should be included.
DR. HEERINGA: Thank you very much. This is obviously a major question in the operation of this model, the mechanical operation of this model and what is implies for the more detailed physiological and other components. I would like to turn to Ken Portier as the lead discussant for this.
DR. PORTIER: Thanks, Steve, I'm glad you asked.
Question A, the table formats are logical, simple implement and clear, one might argue that table 3 could be organized some other way for example with pesticides as the main column heading and exposure types as a subheading, but as long as the data and the relational data base of the type proposed this is just question of how the data base is presented to the reader and is not a reflection of the actual structure of the data base.
I really don't know if the data base even has to be implemented and accessed specifically, the data are relatively straight-forward with the table 2 data being essentially header information for the time

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series data table, table 3A. One could just as easily implement this in SAS (ph) or in Oracle data base systems.
I do understand that LifeLine is primarily based on personal computers and that the development staff have extensive experience with Access, in addition it's a simple task to move the data base from one system to the other, thus if the PBPK/PD model were developed with software that requires an Oracle or SAS or other data based structure the conversion should easily be accomplished from the access structure.
And similarly if the PBPK/PD model is object oriented as was suggested by one of the public commenters it would seem a simple matter to reformulate these tables into data elements for individually based objects.
If on the other hand the PBPK model is stand along code programmed in a traditional programming language there shouldn't be any difficulty in reading the data that way either, so I really don't see anything in this data structure that prohibits it from

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being used by anybody's pet PBPK/PD model.
And Peter MacDonald's comments were essentially the same thing only he did it in two sentences.
For question B are there additional parameter options that should be included, and my take on this is going to be from a statistical problemistic point of view and I'm hoping the other members of the panel will address it from the more data specific point of view.
Tables 2 and Table 3A should be considered

the minimal data requirements for the output file structure. The panel has already discussed the concept of adding genotype information for each individual as an input for future pharmacokinetic information, so that was one idea that came out of the discussion in question 2.

Additional components will depend on how the PBPK/PD model outputs are analyzed and it's recommended that some thought be given to the particular issue as well, so I'm not even worried about what's in the PBPK/PD model, it's just that that

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model is going to produce outputs and we're going to want to do something with those outputs, we're going to want to analyze the output that comes out of that model, and there's potentially going to be parameters that we want from the exposure side to correlate regress or plot against the outputs from the pharmacokinetic model, and if those output parameters are not in that input data base, the one that we're creating here, you won't be able to do that analysis.

So for example in scenarios where exposure is generated for each individual for a short period of time I would append to table 2 the individual's body weight and body height, which by the way are not in that table which is kind of surprising that it wasn't, since these along with gender are the key characteristics that are used by subsequent models to derive most of the flow rates and volumes of table 3B.

The table 3B data might be appended to table 3A if the LifeLine model does the actual calculation of these physiological components, and it wasn't clear in the paper whether the model was or was not going to do it, that might be an actual intermediate model

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itself.

As pointed out in the discussion of question 2 there might be a need to add to table 3B data information on some activity related time series that might be of use in the PBPK model such as the time since initiation of a fat rich model or blood lipid levels or something like that that we haven't looked at the yet. I suspect it will be useful in the final presentation or data analysis of the results to examine some integration of the multiple values potentially output from the PBPK/PD model against things like body weight as well as sex and age. So I can envision a body weight by some kind of absorbed dose model that you want to look that and if body weight is not in the original data set you can't do it.

Additions to table 2 will also depend to a certain extent on the results of our discussions in question 4, for example if the LifeLine model simulated individuals are organized in the percentile classes from which individuals are selected for further analysis in the PBPK model I would expect

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table 2 to include this class score in the output. So for example if I'm running all of these individuals and I decide I want to create bins of a certain kind of exposure from which I'm going to then join individuals and pass them through the pharmacokinetic model, I would want to know what bin that individual model came out of.

Again, final analysis plans drive this request since one can envision wanting to examine a plot of certain integrated PBPK outputs against the associated percentile. One might wish to select replicate individuals from say the 95th and 99th percentiles or percentile bins of the exposure distribution for continued processing, collect the resulting outputs, process them, and then statistically test them to see if enter individual variability and responses had the different percentile classes, swamps out the average level responses that come out of the models, so I'm thinking in the result here you might be wanting to do some kind of analysis of variance to see whether we want to generate things at the 99th percentile or the 90th percentile, and

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you're going to need these class scores to do this. You might want to do blocking on body weight that, I've got some discussion on that as well, that just means one or two factors.

A another driver of the table 2 information depends upon how uncertainty and variability is added to the model, that is how many problemistic Monte Carlo simulation is run. Assume LifeLine does generate the information from table 3B I can conceive of three possible approaches to incorporating stochastic components into the conversion of body weight and height values to physiological flow and volume characteristics of that individual.

So for example right no we have been pretty much been talking about the no stochastic components so to every individual of similar gender, body weight, height, age, sex, ethnicity, you're going to have one set of equations that describes all of these physiological characteristics. So for example the blood volume equation is given here, so if everybody's got the same BH and BW, they're all going to get the same BV, we might want to perturb the mean in which

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case we would add a random component to the end of the equation to add some noise and that would be taking into account this r squared issue that we were talking about, that is uncertainty in the overall fit of the model or you might want to perturb the actual parameters, that would be more of a uncertainty analysis, I mean these regression parameters have uncertainties associated with them and so you might want to generate a situation where the parameters themselves are modified or perturbed a little bit. In

any of these two or three I would want in table 2 the information on what was the perbations (ph) because I can perceive of situations where you run this model and then some really aberrant result comes out and you look at it and you will scratch your head and say why did it do this, and if we don't have these perbations we don't really go back and say I reason is I really blew this parameter up way too much and that was the problem with the model that doesn't represent a real individual, and so we need to be able to track the parameters of any Monte Carlo situation, and this just kind of expands on what Dale was talking about.

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Finally as in the side I can envision a sensitivity analysis of the model components and some future point that goes beyond parameter uncertainty and response to variability but to actual component model form uncertainty, and we were just talking about this so it's not a linear regression, maybe it's a nonlinear regression when we start modeling 12 to 25 year old component growths and we have to go to nonlinear structures instead of one in linear form we now have an infinite number of nonlinear forms, we may want to do some sensitivity analysis there and my take would be that as you build the model the ability to kind of slot in that equation and then pull it out and slot it different in may be very useful, and I would like to see that capability but I don't know what that means for table 2 and 3A and I'm hoping that developers would think about that as well, so that's more than an option.

DR. HATTIS: Well I didn't have anything to add until Dr. Portier --

DR. HEERINGA: He has that effect on people.

DR. HATTIS: And that is in constructing the

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stochastic versions of the taking into account the uncertainties in model form and model parameters there is a trap that you can fall into that you would do well to avoid. I've noticed that sometimes papers in the literature publish some statistics of error on the individual parameter estimates in a regression equation, unfortunately they don't also publish the covariances of those things.

If you just take a Monte Carlo simulation of those parameter estimates you will get nonsense because of the neglect of the covariances. The way that is ideal if you can get the cooperation of the individual investigator is in fact to get the original data set, the full data set and re-estimate the by some kind of bootstrap simulation or otherwise, the confidence limits from randomly selected you can get confidence limits on the model predictions if you have the original data, but if you have only the summary data without the covariances you're not usually able to restrict the original data set and its variation.

DR. HEERINGA: I will just add the way that

that would be done in regression is to take that
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variance/co-matrix variance, you get the Cholesky (ph) decomposition which is essentially the square root of that matrix and then you perturb all of those coefficients as a vector.

DR. EDLER: I feel I go a little bit back now in my first comment. The flow charts you had in your paper are really very transparent and show exactly what's going on with one person and how you store this data and I think that's a very fine job. In real life situations I'm not sure if you thought about that, but you can think of various scenarios how data are really available and want to go into this model. What do you explain was just as run, you run through all of these loops on these sheets and in ten periods of time and you fill that out and so on, so you could do that for just model one person that way.

On the other hand we discussed that also earlier that you could use more aggregate data just one week is always the same and so how will that be built in that model, I couldn't see that not so exactly, so the question is how you get exposure model as a bargain information into an exposure model. And
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another point I got in mind is availability of data of some persons may be just limited either one may have to accept that data are missing or that values have to be summarized, for example some by taking means, so the question is how to specify how missing data will actually be handled or do you want to handle missing data in that program, and if so what would be default values or sources of default values you will use when you handle something like missing values.

Some shorter comments, modeling you're talking modeling I think that's language, modeling is time dependent but actually you think age-dependent. And we also had this discussion around I would trust to repeat it again, the PBPK model will actually be based on differential equations, you go to -- actually if you model them you go to the different equations to solve the differential equations, so this equation must be used in the PBPK model anyway, so I wonder if it would be very difficult to use those dynamic features also in the exposure model for instance if you were on a model for soil contamination and you have a transport model to the humans.
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And I really like a echo what Ken has said at the beginning, I think this data can easily be transformed using pretty cheap software into other systems like SAS or (inaudible) and since universities actually offer SAS as a very cheap price to students it might be just nice to have also SAS files for them just to use them straight ahead.

DR. HEERINGA: Thank you, Dr. Edler. And as I think Dr. Portier has already concluded Dr.

MacDonald's comments in response.
On this question are there any other comments from any other members of the panel?
DR. RYAN: I would just like to reiterate on the last comment and Dr. Portier also mentioned it as well, I just have a statement here regarding the Access data base interface, I say that while offering certain advantages Access does such as a consistent interface, the ability to do a lot of data base work with the stuff that comes out of the exposure and my computer just went away -- okay, now it's back Access comes with a great deal of overhead. If we're talking about a billion observations or something like that

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any overhead that might be put on top of that to handle all of that may be a little bit difficult and I think just a simple output file to be read directly into the pharmacokinetic model is probably the way to go.
Admittedly if we do some of this subsetting it might be of interest in the exposure world, the data bases put together an Access will be useful, but I don't think it's necessary and may end up being a bottleneck overall.
DR. HEERINGA: Thank you, Dr. Ryan. Any other comments?
Is that response -- I neglected with the previous questions, but I'll do it here, is that response sufficiently detailed and covered the points that you want it to?
Thank you to the commenters then.
Let's move onto then charge question 4.
DR. LOWIT: The suggested approach addressed in question 3 will make resource-intensive computational demands making computer run times impractical for regulatory purposes. The LLG white

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paper proposes that not every record generated or processed by the LifeLine model be saved. These limitations will require that model runs be limited to a few hundred or a thousand individuals and that only some fraction of the records be retained by software and used as input to the PBPK/PD model. The process of selecting the records to convey to the PBPK/PD model will require special attention and a transparent prioritization scheme based on explicit criteria. The specific nature of how this will be done could be based on any of several criteria. For example, the exposure software could create a demographic, physiological and exposure history for each individual and tag only those individuals with estimated exposures relative to potency factor adjusted exposures greater than none certain user-defined cut-off for example BMD ten or two, greater than user-defined percentile, for example, 90th percentile. Only those records that were tagged in this way would be included in the interface file that will be

exported to the PBPK/PD model. In this way, only the records that were at the high end of the exposure

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distribution or however defined by the user would be run through that model.

Part A, please comment on the proposal to retain only a fraction of the records generated by the LL model for interface/export to the PBPK/PD model due to computational demands.

And part B, does the panel have any comments or suggestions on the criteria which should be used to select records for input into the PBPK/PD model?

DR. HEERINGA: Thank you very much, again a very important question.

DR. REED: First off I think the idea of coming up with some kind of criteria for selecting on the inflection of data, the exposure data for PBPK input it could be a practical question pertaining to current operation of limitations, we're just talking amongst ourselves with the advancing technology this may not be an issue in the future, nevertheless taking a specific segment of the exposure record for inputting to PBPK model is a viable option as long as the entire record is retained and can readily be called up for additional iterative analysis.

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The criteria for selecting exposure records for PBPK input is inherently dependent on the purpose and focus of the assessment. (Inaudible) desirable that any criteria be not hardwired into the model, instead they should just be options for the user which is to simplify the subsequent PBPK analysis or have specific interests for answering a particular inquiry. Some initial options could be to just focus at different parts of the exposure distribution or it could be just a random draw from the entire distribution.

Discussions to focus a particular fraction of data should be done with great care when the risk assessment (inaudible) still in the learning curve. In fact it is important on the other hand that when the model is available the user should keep track with the data that are put aside because without these records the final results of such analysis would be left without any context especially when fractions of data are as used two or three levels down the road in a cumulative assessment I think that is an important point.

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With that I am also going to read Peter MacDonald's comments and what he has here, he says I don't see how you can reliably predict who will be in a given upper percentile of risk before applying the PBPK steps, theatering to select upper quantiles may be possible after you have a lot more experience with the combined model, but would be prone to error at this point, I would prefer to have a simple random

sample of the total generated population.
DR. HEERINGA: Thank you, Dr. Reed, for your comments and also reading Dr. MacDonald's comments into the record.
DR. LU: Let me provide my response for B first and then go to 4A. I think the output of this exposure assessment model in terms of the number of the data generated is inherent from the nature of this group which of compound which is carbamate, maybe because of short half-life. So which kind of force either the model or the whoever the collector sample focus on very small a shorter time frame you know you have 10 minutes, 15 minutes, or 30 minutes.
So the number that calculate by Dr. Portier

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may not be as much as billion but million would be right number but I would say although those million or billion datas, you know many of them would be just non detectable for any of those carbamates pesticides, I think that leads to the question that whether we should just remove those numbers, those datas and then focus on those detectable concentration, but I will argue that it's important that we re-mend those distribution at the face of exposure assessment model, and then if the platform of data input to the PBPK model is single data input then we may not want to input the zero number because we will have no impact to the PBPK model outcome at all, however if the platform later is basically on the distribution of the data point and that would be interesting to see if we remove those zero exposure data that the distribution at the end of the PBPK model and simulation will be similar to those that may tend to hold distributions.
So to answer the question for A is now what is the limitation and what is the bottleneck. According to the presentation by LifeLine it seems like despite the computation of the PBPK model is the

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bottleneck, so that's why we need to input last number of exploited data, you're shaking your head no, anyway, let me just finish my response.
If we were able to control or make the PBPK model more flexible as you are presenting earlier that there is a 23 organ tissue compartment and you think about those 23 organs tissue compartment which maybe seven or eight are relevant in terms of toxicological impact to the exposure to carbamate and also pharmacokinetically you know make sense and then we can just turn off the rest of those tissue organ compartment by assuming the zero population coefficient then that would speed up the computation, so the limitation may not be as severe as they look like right now, so that would be just my response to question 4.
DR. HEERINGA: There was, somebody obviously nodded or shook their head I guess with regard to Dr. Lu's comment on speed of computation.

DR. CHAISSON: I'm an eternal optimist, but on that kind of an issue between the kinds of things you're commenting with there are other conventions

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we've run into -- let me put it this way, where we come from in terms of modeling with the old clunker PC's and things like that were so much more challenging I think than what we have to do going forward that although I appreciate the hits from this and things like that, that is does instill a fear in us that that will be a bottleneck eventually or that there won't be ways around it or parallel computing exercises and things like that won't be able to be utilized to keep the speed up while retaining.

I guess I personally have more concern about your feelings about the policies and the focus and where we should go with this and I think the mechanics and things shake themselves out, maybe I'm being polyan-ish about this, but I'm fairly comfortable that we will be able keep the speed reasonable.

DR. HARRY: I guess first what I would say is I agree very much with what Dr. Reed and then what Dr. MacDonald had said is that this is going to be an evolving process and I don't think that you can sort of any priority make a statement of how you're going to select your samples until you start getting in and

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working with this.

I also think in Dr. Lu's last comment that when starting to go in and model, again as you learn how to handle the system you may find that rather than having to drop records you're simply not using as many variables as the whole data set has, you don't need to do that, so I think they are going to be handleable and I'm not real sure that I like the idea of setting beforehand that records are going to say I'm only going to look at one particular population, if you start to do that and you are going to have to select, but I think you are going to have to make it very clear what your rationale is for any form of selection of selecting in or excluding out any records when you do this.

As I mentioned earlier I think one of the biggest criteria you're going to have to do is that the quality of the data that you have in there, the confidence that it's correct is the strongest point that you have to select on because this is going to be meant to bring in all the of the data so that nothing is missed, and it is going to be with the modeler's

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responsibility to ensure that they double-check the quality of it as it may be tagged somehow.

I will make a comment that the largest cohort or done under GLP is not necessarily the best data set, so you really need to do the qualitative evaluation of what's there. The other thing that I was concerned about is or just an idea, as it was

brought up about whether you were going to do certain percentiles it is probably not appropriate to do a modeling on children on a whole data set that what you may want to do is to break this up as far as an age component or things that are logical, things that you have questions on, I mean are you going to be concerned about children, you're going to be concerned about adults and you will be concerned about the elderly and we really don't know what those kinetic modeling differences are like across there, this would be an opportunity to hopefully be able to maybe get additional information to understand the dynamics that happen.

DR. RYAN: I have several things in my written comments which really reflect things that have

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already been presented here and I will just say that for the record, and these primarily focus on the answers or the question 4A.

In 4B I actually thought for a little while about what kind of things I as an exposure assessor might be interested in having information about and then figuring well everyone must be exactly like me and they would like that as part of their pharmacokinetic output, and I came up with a few ideas that may be of interest and I will just express them here.

What kind of data would you like to see output, well I came up with several categories. It would be nice if one could just spit out by it hitting a button or something like that the mean or median or some measure of central tendency of distribution of exposure and then to run that through the pharmacokinetic model just to see where things were going to come out. Another thing already been spoken of here just a random selection from among the one billion observations that they might be there, maybe we choose a thousand to run through the

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pharmacokinetic model and they would be chosen in a purely random fashion.

And alternative to that would be some type of ordered selection procedure, you would sort the data then take every 100th observation and sort of a Latin hypercube approach to the sampling strategy. I think that might something of use, values above a certain percentile, this is quite difficult because you're going along keeping track of which ones you're trying to save because it's just difficult to estimate what the 90th percentile was going to be when you only have a thousand observations out of the billion, but you can start to get the idea and make some judgments based on that.

I also thought it might be useful just to take us the middle of the distribution, the 25th to 75th percentile, something like that, similarly values below a certain percentile, people may be interested

in what happens when people just have just a little bit of exposure not withstanding Dr. Lu's statement about well much of these data are going to be below the limited detection, very low values may go through

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the pharmacokinetic model in a different way than very high values, something may saturate, who knows what might happen.

But all in all the ultimate thing is you want this to be flexible for the user, it would be nice to have all these things as a simple check box some place at the front, say we want to get these type of things out but there also should be some way that the user could specify exactly what he or she wants to use as their upward variable. So just including the flexibility I think is important. When I first read this document and read the question I thought that the model that was being put together was going to have something hardwired in whereby you could never get anything out, that was clarified to me in the presentation this morning and I want to make it clear that I understand that that is not the case now, but it would be nice to have some of these features readily available for people so that they didn't have look at the one billon observations but those one billion were still available for them, and I think that's the consideration that most of us when we're

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sitting around talking about this we're concerned about what information are we going to lose and the answer is we don't have to lose anything if we don't want to.

DR. HEERINGA: Any additional comments from the panel on this question?

DR. PORTIER: On A one can view the output from tables 3A and 3B for that matter as discreet representations of time based functions, a large fraction of the time the estimated exposure value is going to be zero, so these are big tables, 23 by 144 for one day with 90 percent zeros, some efforts should be directed toward looking at methodologies for reducing or compressing these the smaller representations. One such method that immediately comes to mind would be wavelet transformation representation, this could dramatically reduce the total storage data needs of the model with probably minimal additional computation needs, so you're taking a big matrix and you're reducing it as a small vector of parameters and you basically have a little compressed, decompressed unit that takes it and brings

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it back and basically it would be a no loss data compression storage.

Experience and sensitivity of the use of these data PBPK models will inform us as to whether the full detail of the 144 observations for data is needed or some loss of signal can be tolerated and if

loss of signal can be tolerated we can actually even reduce that parameterization even more, loss of signal means smoothing out the pattern rather than maintaining 144 discreet points, we smooth it out and parameterize it, the ultimate parameterization being a regression, right, where all your data comes down to a slope and an intercept, everything to two points, I'm not going that far okay.

On B I had results very similar to Dr. Ryan's results, maybe a little bit more operational, for certain types of risk assessments the full distribution of outputs from the PBPK models will be wanted, one needs the flexible approach to selection of individuals, bending approaches linked with sampling and replacement probably represent the most flexible structure. One can classify individuals via

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some metric such as total exposure and then assign them the predefined bins.

You can fix the bin sizes and then just keep track of how many individuals really go into that bin, so you develop probability for the bins and as you fill it bins once the bin gets filled you can have some kind of scheme for possibly replacing individuals as you go through your population. So if you only want to run 1,000 you can assign them to 110 bins and they would be kind of filling and then in a while through one out and put a different one in depending on some other criteria, maybe you want to make sure you get the full body weight represented in each bin, so as you go along you could be monitored.

Operationally that's easy to do, that's essentially a Latin hypercube sampling with post probability replacement and it would give you a way of actually regenerating the whole distribution at the end of the study without having to generate all 10,000 individuals, you could probably do it with, and Dr. Heeringa could probability tell us exactly how many we need in each bin to regenerate the distribution to a

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certain level of accuracy.

DR. HEERINGA: Thank you, Dr. Portier, are there any other comments from panel members?

I would like to add to that. I think that there are a variety of methods that could be used to reduce the data and I think we should look at all the dimensions as we talk this morning too or discussed this morning about the ability within LifeLine particularly to not only retrace data elements but to look at pedigree down to being able to identify this particular observation came from a draw of case 284 in the CFSII. I think you may want to rethink that, I think right now everybody is saying yes, bring all of this data forward at least into this data storage format be it in Access or in some sort of line file or in SAS, but I think that if we look at users, if we burden every user with having to carry all of that

baggage forward if they don't need it, I think that's where we need this handshake between the exposure outputs generalized as you have them already with almost full information and retractability and elements that Ken has mentioned too to be added.

I am concerned that we have to thin about all of the aspects of what we're carrying forward and how it's useful and very honestly every user is probability going to have a different profile of things s they would like to see, so I think sort of starting with this thinking that you maximize the retention of the information upped as you have them in LifeLine up to the point where you produce the exposure profile, but then I think between this exposure model between LifeLine or any other exposure model and PBPK models, as I understand from the specialist there that many of them are probably written, tailored in special software systems you know individualized input structures that I think we need to think about what is the handshake between them and one of the elements that has to come in if you within LifeLine can realistically produce 10 minute increments somebody else and I think and Dr. Lu was getting at it this morning with the carbamates somebody is going to have to take those 10 minute increments and somehow translate those into much shorter interval time profiles and this gets linked to Ken's wavelet notion too, so for some types of compounds that have these short half-lives and quick reactivity that 10 minute increment time data and exposure data is going to have to be modeled out and smoothed out as they see appropriate, so there's really almost a timing modeling that takes place between the exposure delivery and 10 minute increments that you provide and what they feel they realistically need, and some people are going to add those things up over several days or over several hours, and so I think we can anticipate and I think it is one that we haven't talked about, we assume that it comes out of the exposure model and immediately is available to the PBPK model, but I think that as I see it right now and until we standardize and I don't know how much standardization can achieved realistically we probably have to anticipate that there is a processing step in between that and I'm not sure that should be your responsibility with the exposure modeling or should it be left on the side, I mean who reaches over the farthest here to make that link, but I think it is going to be important to think about that as we move ahead.

And so any other comments from the panel. Okay I'm going to turn to the Health Effects Division Staff, are you satisfied with that response?

Okay. I'm going to thank everyone. At this

point I do want to go back to the panel because one of our practices is to allow every member of the panel a final opportunity to make a comment either direct it to one of the four specific questions or to this general process related to the incorporation of the pharmacokinetic modeling into exposure risk assessment and why don't I begin with Dr. Hattis, do you have anything?

DR. HATTIS: I said my say and I think we're done.

DR. LU: I want to make a final comment, we haven't really touched the interface, the link between exposure and the PBPK model. I think that would be a very critical point. I mean from the public comment section the other modeling groups claim that you know this is more like a one-way traffic, they would like to be participate but in a different format, I think

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that would increase the burden of the Agency down the road, but if we can or if LifeLine can come up with interface, again I want to emphasize this, independent on your exposure model, that would be accommodating to other exposure models, so every exposure model the output, once through this interface will be harmonylized and will be useful for the PBPK model, I think if we can do that that would be a great success and I would like to emphasize that.

DR. HEERINGA: Thank you, Dr. Lu, I completely agree on that. But let me ask the panel, I made a statement here that I felt that coming out of the exposure model this policy of maintaining a fairly extreme amount of detail even though it has burdened some storage requirements, I think it is a good idea, now if it becomes unrealistic I think then things have to be called down, but until we reach that point I think that facilities exactly this next step, we have a broad set of data, it's arranged in a way that anybody can access it in a variety of different approaches and different summarizations.

DR. PORTIER: As I was going through the

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document and kind of outlining for myself kind of the overall conceptual model of what we're doing here, the exposure, activities, and everything else, there was a component here called metabolic -- kinetic metabolic activity, and that was a box that wasn't very well explained in the discussion, maybe it's just a phrase, it wasn't a box, but in my diagram it is a box and I was hoping to get a little bit more insight from the toxicologists as to what that is and whether the data coming out of the exposure actually addresses some of the information we're going to need for that component and I'm looking at Dr. Sohn because he looks like he's going to tell me something here.

DR. SOHN: I am not a toxicologist and I will go on record with that first of all. I had that comment in my presentation in fact I missed it so I

didn't make a point and I was wondering how I was going to make that point so thanks.

Obviously the metabolism is rather one of the most critical primaries in the pharmacokinetic model, in fact (inaudible) in some of the reconstructions that I have done it is one of the most dominating ones

and the least known. And if it's your choice to punt to that issue to the pharmacokinetic model developers then so be it, but are you in the process of looking at the data, available data to understand what potential pharmacokinetic metabolism are for various you know chemicals as you move forward.

MR. PRICE: We are very much oriented toward a model that supports exposure to pesticides but the pesticides information is brought to us, we're not doing research on the metabolic factors associated with it, maybe I will take a second response to some of the other issues. When we talked about the genetic components we were more -- it was more practical and more clearly written but it was more in the spirit of saying that once you define a person somewhere in this process the definition of the person that has first established in exposure modeling can be used to guide the selection of genetically based differences of metabolism that may happen later in the PBPK modeling.

We wouldn't actually do that modeling and exposure side, all that would happen later, but we would provide the definition of the human, the subject

who is being simulated in here that would inform and allow people to make a probable decision to assign them to a particular phenotype or other category, that's something that could be more clearly described.

DR. SOHN: Then my response is the component or the parts of the system that is generating parameters for the pharmacokinetic model has generated the volumes and the tissues sizes, my recommendation also consider metabolism as well, whether it's there you're doing it, whomever, but that component it's strikes me as being dangerous to ignore the issue of metabolism there.

DR. PORTIER: And I would say I guess at this point my belief is that they're thinking that between gender, size, and size of components and flow rates you have enough information to specify some general metabolic capacity, metabolic activity level for an individual and that's probably the level of thinking you're at right now and my concern was on the exposure end in the sense of is there another component here that would be more critical to metabolic then gender, size, and flow rates, it's something else that we're

missing.

DR. CORCORAN: It would be genotype.

DR. PORTIER: Well I mean that's, how about enzyme --

DR. CORCORAN: I think the ability to get at that metabolic phenotype or (inaudible) type the individual with the data set that the LifeLine model uses would be virtually impossible, and not only would it be difficult to get there but was generated and might actually bring you the opposite direction in the accuracy of what you're trying to prescribe, may make it dangerously wrong. These have be approached either stochastically or perspectively with not only genotypic information by phenotypic information which becomes to proteomics (ph) and other omic technologies which go in my view far beyond the scope of what we really can approach today and probably for some time.

DR. MACINTOSH: I suspect that we saw some of that in the white paper, I mean the recognition, what I mean is the recognition of the LLG group that those areas were outside of what they were talking about. For example when I was commenting earlier I said do we

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want section about metabolic or something -- physiologic variability totally ignored absorption metabolism, elimination, just even though those ideas had been introduced earlier they're ignored there, so I would suggest that maybe a figure or a table or something that attempted to elucidate what parts would be considered by the exposure model explicitly versus parts that wouldn't be considered at all and parts that might be in between or you can kind of link from one to the other, that might be helpful.

DR. HEERINGA: I like that idea too, and also combine that remember with this flow diagram about what the ideal information needs would be, where those data gaps exist and when they might likely to be filled and that sort or prospective way of thinking about how this might evolve. I think that's the critical issue as to how you are going to partition these responsibilities between your production of exposure modeling outputs for individuals in a representative population and then the pharmacokinetic models, inputs of those two models.

DR. CHAISSON: Before Dr. Heeringa, before

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you conclude this we would like to just say thank you so much to the panel, we got great comments and we appreciated the this kind of conversation, it was exactly what we were hoping for and we are very, very pleased that everybody still had the energy to put this kind of deliberation into it and we do appreciate that very much.

DR. HEERINGA: On behalf of the panel I want to thank you. I want to do one last thing here and Dr. MacDonald who did have to return to Toronto, one additional comment that he wanted and this is Peter's standard mantra, but I think it's important to put in here too and I'm going to quote, it's not enough to wait for bug reports from users, there needs to be an ongoing code audit, open code facilitates this and

perhaps some users are qualified to review the code for specific modules and may be possible to distribute the task over these users and then as the model gets more complex and more and more subjective assumptions and arbitrary decisions will become lost within it. Somehow we will have to remain aware of these and improve on them as new information becomes available.

I mean obviously we're building complex systems and Peter is just sort of bringing us back that we have to, even though they become complex it's still not an excuse for not sort of maintaining you know sort of a vigilant oversight on it.

MR. PRICE: We couldn't agree more and I think my response earlier which I believe could have been a little bit more thoughtful, we have -- one of the cornerstones of the LifeLine Group is to make our code publicly available, anyone upon written request can receive a copy of code for the purposes of verifying it and we're very attracted to the idea of and coming up with a system to apportion out to have people and the appropriate individuals perform a code review.

DR. HEERINGA: I don't see any additional comments I guess I am going to turn back to the EPA staff, Health Effects Division.

DR. PERFETTI: Well it's over and once again I just want to thank the panel, as Joe said this morning you probably all deserve a metal of honor or valor, once again we came to you for counsel with

respect to this topic and the previous two topics and once again we've some great insights and some great advice from you. Again, on behalf of LPP, LPP, OSCP and OPPTS we thank you very much.

DR. HEERINGA: All those acronyms you have to have them memorized. Thank you very much. Before we close I'm going to turn to our designated federal official, Joe Bailey, do you have anything to add, Joe, in terms of this.

MR. BAILEY: Just a reminder that we anticipate having a report completed for this session in six to eight weeks, so that would hopefully be mid-January or late January and thanks to the presenters today, thanks very much Dr. Heeringa for chairing the meeting today, and thanks very much to the panel for enduring throughout this week to those of you who have been here for the four days and thanks to those who joined us just for today's session, and we look forward to seeing you all in February.

DR. HEERINGA: With that I think I am going to draw this meeting to a close and wish safe travels to everyone. And for those of you who are panel

members who have a few minutes before you have to catch your flights why don't we just convene back in the room, but if you need to make a trip to the

airport now, again safe travels and hope to see you all again.

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