THE LIFELINE GROUP

Designing Exposure Models that Support

PBPK/PBPD Models of Cumulative Risk

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Definitions

Absorbed dose

The amount of a substance that enters an individual's body as a result of passing an exposure/absorption barrier (e.g. skin surface, alveolar wall or the surface of the gastrointestinal tract). Also referred to as the internal dose.

Aggregate exposure

The total exposure from all sources (excluding occupational exposures) to a single pesticide by all routes of exposure.

Contact dose

The amount of pesticide presented to an exposure/absorption barrier and available for absorption.

Cumulative exposure

The total exposure from all sources (excluding occupational exposures) of multiple pesticides operating by a common mechanism of action.

Dose

The amount of a substance available for interaction with metabolic processes or biologically significant receptors after crossing the outer boundary of an organism. It can be described as potential dose, contact (applied) dose, absorbed dose, internal dose, delivered dose and target (biologically effective dose)

Eating event

A collection of food items recorded by an individual as being consumed at a particular time of the day or at a named eating occasion (i.e. lunch).

Exposure

Contact of an organism with a chemical, quantified as the amount of chemical available at exposure/absorption barriers of the organism and available for absorption.

Exposure/absorption barrier

Any of the exchange barriers of the body that allow differential diffusion of various substances across a boundary i.e. skin surface, alveolar wall or the surface of the gastrointestinal tract.

Metrics

Quantitative measures of exposure or dose that specify the compartment or location of the pesticide (on the skin, inhaled, or crossing the GI tract, or etc.) and the units that the measure is expressed (mg, mg/kg, ppm in air or water).

Exposure history

A description of an exposures and resulting doses that occur over a specific period of time. Composed of multiple time steps.

Food item

A description of a food (with a defined recipe of ingredients) in its edible form.

Internal dose

See absorbed dose.

PBPK/PD model

A model that is a combination of PBPK and PBPD models.

Pharmacodynamic model

Quantitative models of measurable effects of pesticides typically at the tissue or cellular level.

Pharmacokinetic model

Quantitative models of the intake, movement, metabolism and excretion of pesticides in humans and other animals.

Person Oriented Model (POM)

A model of exposure produced using a modeling architecture that places the person central to model design. Contrast to source-to-dose models.

Simulation model

A quantitative model that characterizes exposure and dose by modeling the uncertainty and interindividual variation of those parameters that determine exposure and uptake.

Target (biologically effective) dose

The amount of pesticide that reaches the tissue or compartment where an effect occurs.

Time step

A period in an individual's exposure history that is sufficiently short that the inputs to an exposure or dose equation can be treated as constants.

1. Introduction

The Environmental Protection Agency (EPA) is charged with assuring the safety of pesticides by regulating their use in the United States under the Federal Insecticide, Fungicide and Rodenticide Act and by setting tolerances for all crop commodities (domestic and imported) under the Federal Food and Drug and Cosmetics Act. In assessing the potential health risks associated with exposure to pesticides, attention has historically focused on single pathways of exposure (e.g., from pesticide residues in food, water, or residential/non-occupational uses) for individual pesticides, and not on the potential for individuals to be exposed to multiple pesticides by all pathways concurrently. This changed in 1996 with the passage of the Food Quality Protection Act (FQPA) which required the consideration of human health risks resulting from concurrent exposures from multiple sources and routes of exposure for dietary and non-dietary, non-occupational exposures (aggregate exposure) and by the concurrent exposures to all pesticides acting through a common mechanism of toxicity (cumulative exposure). The FQPA also required attention to potentially vulnerable population groups.

In response to this requirement, the Agency developed guidance for performing aggregate and cumulative risk assessment (EPA, 2001; 2002a). In 2002, EPA performed the first cumulative assessment on the organophosphorus (OP) pesticides (EPA, 2002b). As part of the assessment, The LifeLine Group Inc. (LLG) was hired to develop Version 2.0 of LifeLine™ and to use the program to perform an assessment of the OP pesticides (LifeLine™, 2002a).

Over the past twenty five years, exposure assessments conducted by the Office of Pesticide Programs within the EPA evolved from calculation of the exposure presented to the “average American” for lifetime average exposures to assessments of full distributions of possible exposures to individuals within defined population groups over variable time periods. The cumulative risk assessment of the OP pesticides (EPA, 2002b) stands as the most sophisticated attempt to date to realize the goal of the FQPA. The assessment achieves many elements of an aggregate, cumulative assessment for the general population of the United States. It assesses exposure experienced by individuals of all ages via multiple routes of exposure on a daily basis. To achieve consideration of concurrent exposure to multiple organophosphorus pesticides, the Agency used a Relative Potency Factor (RPF) approach, as explained in detail in its guidance documents. This approach accounts for the variance in the potency of each pesticide by mathematically comparing the potency of the pesticides using a common toxicology endpoint. The RPF is defined as the ratio of the potency of each pesticide to the potency of an “index chemical”. Summation of the RPFs that are produced for each of the OP pesticides allows the estimation of an equivalent total dose of the index chemical.

Exposures to multiple OP pesticides can now be evaluated in terms of a dose of one equivalent pesticide; thus, the cumulative risks estimated in the OP assessment were determined by an aggregate model of the total dose of the index chemical. By performing this conversion at the beginning of the exposure process, the OP assessment allowed EPA to use existing aggregate exposure software to perform the cumulative assessment.

In the N-methyl carbamate assessment, EPA is proposing to take the next step in technical improvement of the exposure and risk assessment science. This exposure assessment will independently determine and track the route specific cumulative doses of each pesticide that occur from exposures to dietary and non-dietary sources. The approach will not require the collapsing of these pesticide specific doses into a single dose of an index pesticide. The approach will instead use the pesticide specific doses as inputs to a physiologically based pharmacokinetic model PBPK model and calculate the internal or target doses of each pesticide. In order to support such modeling, the exposure assessment must be extended in two ways. First, the exposure assessment is modified to consider time units of hours, or minutes, instead of days. Second, the exposure assessment is expanded to define not only the doses received by the simulated individuals but also the physiological parameters of each modeled individual. In this way, the dose and physiological information are based on individuals who have a consistent age, sex and activity level.

Finally, the internal doses from the PBPK models are provided to another type of model, the physiologically based pharmacodynamic model (PBPD). This model applies information on the effects of the pesticides (and their metabolites) on the cellular or tissue level. Processes included such as binding and release of substances to receptors, the resulting effects and recovery from the effects. The outputs of these models provide a basis of the determination of whether an “injury” occurred. Because of the close linking of PBPK and PBPD models, they are referred to as a combined (PBPK/PD) model. EPA will employ PBPK/PD models such as those under development by EPA’s Office of Research and Development.

EPA tasked The LifeLine Group (LLG) to develop a new approach to deliver appropriate exposure metrics to the PBPK/PD 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.

This report presents the fundamental approaches and logic for the required changes to the existing exposure assessment methodology of the LifeLine™ software. The concepts are generic, but the technical approaches are specific to the LifeLine™ software. In order to explain the approach and to provide a

framework for the logic employed in this task, this report begins by describing the data requirements of a PBPK/PD model; the report then briefly reviews the state of existing exposure assessment models and their outputs and presents a general approach of the how LifeLine™ exposure simulation model can be adapted to meet the needs of any PBPK/PD model of cumulative risks. Finally, the general approach is shown to be applicable to the specific modeling needs for the N-methyl carbamate pesticides.

2. Accommodating the Pesticide's Characteristics in the Conceptual Design of Exposure Models

The characteristics of the pesticides under consideration influence the calculation of exposure and of dose and risk in two ways. The first way is the direct application of pesticide specific information within a given model. For example, in considering exposure to a pesticide used on crops, the pesticide specific values for residue concentrations are entered by the user and applied to the calculations of dietary exposure estimates. Second, the overall methodology and design of the model should accommodate pesticide specific characteristics as well. For example, if the relevant toxicological endpoint for risk assessment is exhibited only after long durations of consistent exposure, exposure averaging techniques over variable time intervals should be a possible calculation choice for the model user. The model should be sufficiently flexible to allow the user to incorporate the relevant values of potency and relevant exposure durations for the specific pesticide.

Exposure models deal with temporal patterns of exposure using the concept of a time step. Ideally, a time step is the period of time sufficiently short that exposures can be represented by time invariant values. However, the shorter the duration of a time step in the model, the greater are the computational demands in that model. In addition, in many instances, data that would allow the definition of the variation of dose on a fine time scale are not available. As a result, models calculate longitudinal exposures using time steps of a day, a week or a year. In these instances, the exposure is expressed in terms of average exposure over the period.

N-methyl carbamate pesticides have a number of characteristics that influence the design of both the exposure and PBPK/PD models of cumulative risk. These include the rapid binding and release of the compounds as well as reversibility of the cholinesterase inhibition and the rapid metabolism of the active moieties. Because of these characteristics, it is likely that the effects from a dose of a pesticide in this class will persist only over short periods of time. These characteristics suggest that the toxicological effects that occur from a series of exposures on a given day would be limited to that day and would not persist into a second day. This in turn suggests that the temporal framework for the assessment of cumulative risk for this group of pesticides could be limited to a single day. However, without specific empirical data to confirm this, it is prudent to build the model so that it can handle any carry-over time that is warranted.

There is also data indicating that the time to peak exposure via the oral route is considerably shorter that from the dermal route. These characteristics require that the exposure software define exposures on a finer time scale than a single

day and has the ability to define time-correlated exposures across sources and routes of exposure.

It should also be noted that other pesticides or classes of pesticides that operate by different mechanisms might require modeling over longer or shorter periods. Therefore, this report will develop an approach that can also be applied to longer longitudinal periods than a single day and where the duration of the time step required can vary from durations of less then one day to multiple days.

3. Meeting the Needs of PBPK/PD Based Models of Cumulative Risk

The goal for the LifeLine™ exposure assessment model is to provide the appropriate support to the PBPK/PD model of the cumulative toxicological effects posed by N-methyl carbamate pesticides. The initial portion of the PBPK/PD model is a PBPK model for the various pesticides. This PBPK model translates the history (or temporal pattern) of the route-specific exposures of each pesticide received by an individual into a history of the concentrations of the pesticide (and relevant metabolites) in the relevant compartments of the body (target doses).

PBPK models use three different types of information. The first type of data is the relevant physiological characteristics of the individuals being simulated and how those characteristics are influenced by the activities of the individual. The second type is compound-specific data on the absorption, distribution, metabolism and excretion (ADME) kinetics and metabolism of the individual pesticides and how they vary across individuals in the population of interest. Finally, PBPK/PD models utilize time-specific, route specific estimates of exposure.

The PBPK/PD model under development by the EPA's Office of Research and Development (ORD) is not yet available for inspection and discussion. LLG has collaborated with the ORD development team to identify common approaches and definitions and to assure that the concepts developed for the exposure model amendments will accommodate the needs of the PBPK/PD model. The discussions about PBPK/PD in this report are developed by the LLG and are not meant to represent the technical documentation of any ORD model.

3 a. Relevant Physiological Characteristics of the Exposed Individuals

PBPK/PD models require information on the physiology of the individual and how an individual's physiology changes over time. This physiological information includes:

1. The volume of each compartment in the PBPK/PD model;
2. The cardiac output;
3. The fraction of the cardiac output for each compartment; and
4. The alveolar ventilation rate.

The values of these parameters vary from one individual to another and within individuals as a function of their level of physical activity at a given point in time. The values of these parameters are correlated with the estimates of the doses that the individual receives because age and gender influence both exposure

opportunity to pesticides and the physiology of the individual. To address this correlation, the PBPK/PD models must be provided descriptions of the individuals' physiology that are consistent with the assumptions used in the exposure calculations. Thus if the model simulates the exposures for a three year old playing on the lawn, then the physiological parameters used in the PBPK/PD modeling must be consistent with those of an active three year old.

The values of the physiological parameters for an individual are also correlated. Values for one compartment will be correlated with values for another. An above-average body weight and height implies that the compartment volumes of the individual will be larger than average and that the alveolar ventilation rate and the cardiac output will also be larger than average. This kind of correlation must be captured in the inputs to the PBPK/PD model.

While the volume of the compartments are constant over time periods of a few hours or days, the cardiac output and alveolar ventilation rates are not constant. Both the cardiac output and alveolar ventilation rate increase with the activity level of the individual. As a result, the values for these parameters must be specified over time as a function of the activity levels of the individual at various points in time during a single day. To a lesser extent, the compartment-specific fractions of cardiac output are also affected by level of activity and from behaviors such as eating. The temporal patterns of these time-varying parameters are also highly correlated with each other. Factors that influence one parameter will tend to influence some or all of the parameters.

3 b. Kinetic, Metabolic and Capacity Parameters

The second type of information used in PBPK/PD models is the rates of metabolism and partitioning of the specific pesticides. These parameters also vary across individuals as a function of age, gender and genetic variation. LifeLine™ software defines the gender, age, race and ethnicity. These data can be used within the PBPK/PD model to select the values for these parameters.

The pharmacodynamic model for the N-methyl carbamate pesticides has not been finalized but is expected to include the concept of capacity or tolerance to the effects of the compounds. Tolerance to the pesticide's effects is likely to vary across the population and may differ across ages and gender. If this is the case then gender, age, race and ethnicity may be useful for predicting values for this parameter as well.

3 c. Data on Exposure and Dose

i. Matching LifeLine™ Outputs to PBPK/PD Model Inputs

Exposure to pesticides is a multi-step process that takes the pesticides from the environment in which an individual breathes, consumes food and water and contact-surfaces, ultimately, to the target organ where the effects of interest occur (EPA, 1992; EPA, 1997). Exposures to pesticides in the environment occur by dermal, oral or inhalation routes of exposure. As a pesticide passes from the environment onto and through the skin, or is ingested or inspired and absorbed, the concept of exposure becomes a concept of dose. The relevant metrics change from concentration in the environmental medium to route-specific contact dose (on the skin, in the gut following oral exposure or in the lungs following inhalation exposure) to absorbed dose (in the blood, in individual organs or at the tissue level).

This process requires a clear description of each of the steps on the process. Such description requires common definitions of modeling concepts, terminology and measures of exposure and dose (metrics). For example, dermal exposures can be described in terms of:

- Dermal loading (the average mass of pesticide in dirt, dust and oil on the skin and the area over which it occurs) during a time step;
- The average mass of pesticide in direct contact with the skin during a time step;
- The mass of pesticide that is absorbed by the stratum corneum in a time step;
- The mass of pesticide that is absorbed by the dermis in a time step; or
- The mass of a pesticide that reaches the circulating blood supply in a time step.

Doses from exposures that occur by the oral and inhalation routes also have multiple descriptive options. No particular descriptive option is inherently correct or incorrect.

As the LifeLine™ and PBPK/PD models interface and the output of LifeLine™ becomes the input to the PBPK/PD model, the values produced by LifeLine™ must interface correctly, neither presenting a gap in the process nor duplicating a process modeled in the PBPK/PD model. Thus, for example, if the PBPK/PD model includes a quantitative model of the process of dermal absorption, then the exposure must estimate the amount of pesticide that reaches the surface of the skin and the duration of time over which the pesticide remains on the skin. If the PBPK/PD model does not consider the dermal absorption process, the exposure assessment model must include algorithms representing absorption through the skin to provide the absorbed dose resulting from dermal exposure. It

is critical to recognize that the input exposure metric may vary with different PBPK/PD models and to have the capacity to provide what is required. More discussion of the impact of these factors on the interface is offered in the last sections of this document.

This “matching” of the metrics and exposure/dose definitions between linked models is a critical issue and often complicated by the variable use of these terms by different communities of scientists. The definitions including those of exposure and dose used in this report are presented in the beginning of the report and are meant to clarify the concepts discussed in this report and be consistent with definitions used by OPP. They may differ from those used by other scientific groups.

PBPK/PD models characterize the movement and transformation of pesticides in the body. Thus, the PBPK/PD models require information on the mass of the pesticide that enters the body. This information delivered from exposure models should include:

- The amount that enters by each of the three routes of exposure;
- Exposure or dose metric appropriately “matched” to the definitions of exposure/dose used in the PBPK/PD model;
- Exposure histories of the simulated individuals over time;
- Time steps appropriate to the pesticide family (for N-methyl carbamates this would be units smaller than daily); and
- Separate and correlated estimations of route-specific exposure for each pesticide during each time step.

ii. Establishing the Time Step and Exposure History

The timing of all exposure events for all routes for all pesticides must be placed in a consistent timeframe. The timeframe must be sufficiently detailed to be appropriate for the mechanism of action relevant to the pesticides under consideration. To be relevant to the mechanism of action, the timeframe must accommodate modeling of the time course of pesticide delivery to the target tissue, expression of the toxicity mechanism and mechanics of recovery.

The level of detail in an exposure assessment is defined in terms of the duration of the averaging period of exposure. Historically for pesticide exposure assessment, averaging lifetime exposure periods have been used for cancer risk, one year periods for chronic effects and one day periods for acute effects.

PBPK/PD models also deal with doses as a sequence of exposure events. These events have a specific duration and are referred to as “time steps”. This allows the PBPK/PD models to predict the time course of a pesticide in the body as a result of ongoing exposures. These sequential measurements represent the

"exposure history" of the individual. As discussed above, some pesticides such as the N-methyl carbamates exert their effects via mechanisms requiring short periods of time. As a result, PBPK/PD models require an exposure history with time steps much shorter than one day.

The optimal duration of a time step will vary with the mechanism and properties of the group of pesticides. To accommodate the myriad of pesticides and toxicity mechanisms involved in pesticides, models must at least be able to accommodate short time steps and be able to average those time steps over multiple periods to produce metrics of the appropriate duration.

In each time step, the exposure software must determine the route specific doses for each of the pesticides in the assessment. If there were 10 pesticides to be modeled, then each time step would have 10 doses (one for each pesticide) and three route specific doses (dermal, oral and inhalation). This will result in 30 doses per time step. If the time step is 10 minutes, then there will be 144 time steps in a day or 4,320 doses. Since the software used in the OP cumulative assessment only modeled three one-day route specific doses per day, this shorter time step approach generates more than a thousand fold increase in the exposure assessment metrics.

4. Current Exposure Assessment Models: A Brief Overview

Current exposure software programs used by OPP/EPA programs integrate exposures from food, drinking water and residential non-dietary, non-occupational sources to assess acute, short term, intermediate term and long-term/lifetime exposures. All of the models produce exposure estimates in metrics tailored to the risk characterization methodologies employed by EPA (such as the MOE, % RfD and lifetime cancer risk probabilities). The models also place the estimates of exposure into some form of chronological framework. The models typically model time steps of a single day using databases conveniently structured over exposure events expressed in terms of days or subunits of days. This approach has paralleled the toxicology metrics for most toxicological endpoints where effect has been expressed as a function of exposure or dose over one or more days. All of the programs deal only with a single pesticide at a time. As previously discussed, this is true even for the programs used in the OP cumulative risk assessment. Cumulative exposure assessment for these chemicals was achieved by first converting the individual pesticides into equivalent doses of an index chemical. The models provide route specific exposure metrics that are used to support the route specific toxicology and risk characterization methodologies such as the MOE and %RfD. Finally, in various ways, the exposure assessment programs identify some physical and demographic characteristics of the simulated individuals in the defined population under consideration. Demographic information is sometimes limited to age and gender.

The earliest design of the LifeLine™ software architecture was influenced by the recognition that aggregate and cumulative exposure assessment software programs should be able to provide the types of data required by PBPK/PD models including the essential route specific exposure estimates since this application would be required in the future. The LifeLine™ software already has the basic modules that can be enhanced to provide the information required by PBPK/PD models.

4 a. Capabilities Required for Supporting PBPK/PD Modeling

Based upon the above sections there are four areas where exposure models must be enhanced in order to support PBPK/PD modeling in the assessment of cumulative risk.

1. The models must be restructured to provide real pesticide-by-pesticide cumulative exposure assessment rather than using a single RPF approach to represent multiple pesticides.

2. Time steps must be redefined to present exposure metrics as a function of hours or minutes rather than days.

3. The physiological characteristics of the exposed individual must accompany the exposure values for each time step.

4. Finally, the interface between the exposure model and the PBPK/PD model must be fashioned whereby the information is transferred without losing the interconnections of multiple pesticide, multiple route exposure values for a coherent series of time steps for each individual with the relevant physiological and demographic identifiers. This interface must faithfully maintain the continuum from the media concentration values to the target tissue doses without creating gaps or overlaps, as previously discussed. These are additional factors that must be addressed in the design of the exposure database if an acceptable interface is to be built between the models. The interface is discussed in more detail in the last sections of this document.

The following section of the report outlines an approach that achieves these four goals.

5. Development of a New Version of the LifeLine™ Software for the Support of a PBPK/PD Model of Cumulative Risk

This section of the report presents a detailed description of how the current version of LifeLine™ software (Version 2.1) could be enhanced to provide the inputs required by PBPK/PD models such as that being developed by ORD/EPA. LifeLine™ software for exposure and risk characterization has been used by EPA, other international federal and state regulatory agencies, stakeholders, academia, and research scientists since its first release in late 2000. Version 2.0 was used to characterize the cumulative risks of the OP pesticides (LifeLine™ 2002) and has been used in the Agency's Voluntary Children's Chemical Evaluation Program (ACC, 2003). The software has been the subject of Science Advisory Panel (SAP) reviews in 1999, 2000, and 2001.[1]

This section of the report begins with a review of the design of the LifeLine™ software's architecture—the critical element to consider for the modification approach. The Technical Manual for the LifeLine™ software, available from the LLG web site[2], provides a detailed description of the model's architecture, databases and operating algorithms. This report discusses those elements necessary to consider the framework for desired modifications for supporting PBPK/PD models of cumulative risk and details of the modifications. The section concludes with a discussion of how to convey the data from LifeLine™ to the PBPK/PD model.

5 a. The Current Framework of LifeLine™ Software

LifeLine™ software was designed from its very beginning to support assessments of cumulative risk (LLG, 1999, LLG 2004). The design of the software is consistent with Agency guidance for performing aggregate and cumulative assessment (EPA, 2001; 2002a).

i. POM Models

LifeLine™ belongs to a class of programs called Person Oriented Models (POM). These models place the design focus on the individual receiving the exposure rather than the exposure sources (Price et al. 2003a). Figure 1 is a flowchart of the basic components of a POM. These models begin by defining the individual's characteristics. These characteristics are those aspects of the individual that

[1] All versions of LifeLine™ software are made publicly available to all stakeholders without charge by LLG. LLG is a 501 (c)(3) not-for-profit corporation created for the development and public dissemination of risk assessment software and related materials.
[2] www.TheLifeLineGroup.org

influence the probability of occurrence of an exposure opportunity and the magnitude and duration of the exposure resulting from that occurrence. The characteristics could include the individual's body weight, diet within a given time period, activity patterns, residence, location (region of the country) and season of the year. LifeLine™ utilizes a library of person-oriented databases to create the distributions of parameter values. This provides a framework to express interindividual variability for the population of interest.

Once the individual's characteristics are specified, the model enters the *Exposure Event Loop*. In this loop, the POM systematically determines if the individual is exposed to any of the possible sources. Examples of possible sources are the diet or a series of microenvironments that the individual encounters within the time step. If the model determines that an exposure opportunity has occurred, the model runs the appropriate source-to-dose model and calculates the magnitude of the exposure or dose. The series of exposure opportunities for a given individual are consistent with the characteristics of the individual, the point in time and with each other. This is achieved by defining each exposure opportunity based on the characteristics of the simulated person, established at the beginning of the process. This yields temporal consistency in the estimate of aggregate doses for a pesticide. Note that if such consistency is not established within a model, the inconsistencies magnify as the model considers multiple pesticides with route-specific exposures.

Once the model has calculated the exposures or doses that result from each source, the information can be saved as part of an exposure history for that individual and that day. This exposure history can be used in a variety of subsequent analyses[3]. The POM then repeats the process for other individuals, assigning different characteristics by re-sampling the distributions of interindividual variation. This modeling of multiple individuals happens in the *Individual Loop*.

LifeLine™ Version 2.1 currently creates a longitudinal model of individuals' daily exposures over an 85-year life span. The model provides route specific estimates of daily doses from diet, drinking water and residential uses of pesticides[4]. Figure 2 presents the basic design of Version 2.1.

LifeLine™, as with all POM models, begins with a definition of the exposed individual and his or her characteristics on that day. As part of this definition, LifeLine™ assigns the individual a record from the US Department of Agriculture's Continuing Survey of Food Intakes by Individuals (CSFII) and a record from EPA's National Human Activity Pattern Survey (NHAPS). The selection of the records is based on a consideration of factors such as the individual's age, the season of the year and day of the week.[5] The model then cycles through each food consumed on that day using the *Dietary Exposure Event Loop*. The exposure from the consumption of each food item is determined based on the amount of the food consumed and the residues possibly in or on the food. The same process is used for each instance when drinking water is consumed. The exposures from all consumption events are summed to yield the

[3] Such as determining the highest day's exposure for an individual in a season or a year, or to calculate the average daily dose over a season, year or other specified time period.
[4] Residential includes exposure to pesticides during use and from post-application exposures. Sources of pesticides include food, drinking water, indoor products, outdoor products, public health exposures (vector control) and residues on golf courses.
[5] Details about data binning and construction of the distributions of values available for this process are given in the Technical Manual for LifeLine™ and available from the LLG web site.

total dietary exposure presented by the exposure opportunities (eating events) on that day.

Once the model has completed the calculation of the dietary exposure, it moves to the second exposure event loop, the *Non-dietary Exposure Event Loop*. In this loop, the model cycles through each microenvironment and activity in the NHAPS record. If a pesticide residue is present in the microenvironment and the individual interacts with the residue (as represented on the NHAPS record), then the model determines the exposure presented and the route (or routes) by which the exposures are presented. After the evaluation of the last microenvironment and activity portrayed in the NHAPS record, LifeLine™ totals the exposure presented from each microenvironment by each of the three routes of exposure to provide daily route specific estimates and the daily aggregate exposure. These calculated exposure metrics are saved for use in subsequent analyses.

Once the calculations are saved, the model moves to the next day in the individual's life. This occurs in the "day loop". The day loop begins by updating the characteristics of the individual, pesticide usage probabilities and the residues in the individual's environments. The two exposure event loops are then repeated. This process continues until the exposure period of interest to the user is complete. Version 2.1 will simulate an individual for durations of one year to 85 years

The entire process is repeated for every individual assigned to the population of interest. LifeLine™ accommodates calculations for up to 100,000 individuals within a population of interest (the general US population or a defined subgroup of that population) as specified by the user.

This LifeLine™ framework provides many functional capabilities necessary to calculate the exposure metrics relevant to PBPK/PD models. These capabilities include:

- Definition of the exposed individual in terms of
  - Race;
  - Ethnicity;
  - Physiology
- Definition of the characteristics of the individual's source of exposure
  - Sources of exposure
  - Route specific doses
- Definition of exposure history and
- Definition of temporal changes in demographic and physiological parameters and linkage of these parameters to the activity profiles, exposure opportunities, and estimates of exposure and dose (magnitude, route) for a time step of a day.

These capabilities provide a robust starting point for the design of a new version of LifeLine™ that can meet the needs of the PBPK /PD models.

5 b. Changing the Time Step from One Day to a Shorter Time Interval

As discussed in the prior section, while LifeLine™ calculates the exposure from multiple exposure events over the course of a day, the program sums the doses from the separate events to yield a daily exposure value. With this approach, the time step for the exposure history of the individual is one day. The LifeLine™ framework can also support estimates of exposure for periods shorter than a day. As discussed below, the LifeLine™ framework can accommodate as short a time step as the analyst desires. The practical lower limit on the interval for the time step is imposed however, by the structure of the databases on which the exposure model operates. Temporal information directly or indirectly supplied by the data sets accommodates daily, hourly and to a limited degree sub-hourly time steps. Rappaport (2003), in a review of the work of Roach (1977), points out that many of his early concepts have been borne out by more recent research. In the area of air sampling in the workplace, Roach discussed the appropriate duration of exposure measurement for fast acting chemicals, i.e. those which have a $T_{1/2}$ in the order of 0.5 to 1 hr. Too long a sampling time (exposure metric) would not accurately reflect the maximum tolerated concentration. He showed that selection of an averaging of $0.3T_{1/2\ avoids}$ this problem. Since the $T_{1/2}$ for orally dosed carbamates, as represented by carbaryl, is in the range of 0.5 hr, and the data support peak exposures rather than AUC, Roach's approach is applicable, and a sampling time of 10 minutes would be appropriate. Additionally, there are data in CSFII for consumption of a snack, and LLG believes that inference of a 10 minute time interval for eating duration is reasonable.

The following section presents a discussion about the compromises and derivations associated with such data structuring. Shorter time steps appear to be impractical given the presently available databases.

The tasks necessary to create shorter time steps are as follows:

- Create a user interface to define the duration of the exposure history and the duration of the time step;
- Restructure the NHAPS and CSFII data to appropriate time-related data values.
- Reconcile the conflicts between the NHAPS and CSFII temporal information units;
- Revise the day loop framework; and
- Track and manage the exposure assessment outputs.

Design of User Interface for Exposure History and Time Step

The toxicology of the N-methyl carbamate pesticides presents several issues that influence the design and requirements of the PBPK/PD models of cumulative risk. These pesticides rapidly bind to receptors in the target tissues. The parent pesticides are rapidly metabolized and the receptors are rapidly cleared. Thus, the mechanism by which the pesticides cause the effects on which the cumulative risk is based and the mechanism of recovery from the toxic effects occur over short time intervals. If an adequate number of contiguous time steps occur with no new exposure events, complete recovery of the target tissue is expected. If no exposure opportunity is introduced during a night's sleep, the effects of this class of pesticides will not persist into the next day. This implies the assessment of cumulative risk for this group of pesticides can be limited to a single day. However, the rapid mechanisms of receptor binding and clearance will be better reflected in a model employing a finer time step scale than a single day.

As previously explained, the scenario presented by these N-methyl carbamate pesticides is not universally applicable to all classes of pesticides. Therefore, this report will outline an approach that can be applied to longer periods than a single day and where the duration of the time step can vary from durations of a few minutes to one day. Therefore, the new version of LifeLine™ will allow the user to specify the duration of the exposure history and the duration of the time step in the exposure history.

Restructure the NHAPS and CSFII Data to Appropriate Time-Related Data Values

There are two databases in LifeLine™ that provide temporal information with scales of less than a day, the CSFII and the NHAPS. The CSFII provides daily dietary records for each person with detailed temporal information linked to each eating event of the day. Each eating event of the day is recorded noting the hour and minute of the eating occasion, the foods eaten within that event, the location of the eating event, the amount of each food eaten and the demographic information about the consumer. In addition, the consumer can classify the event as a major meal (breakfast, lunch, dinner) or as a snack event.

The CSFII does not include a measure of the duration of the eating event. Using the consumer's categorization of the eating events and a system of classification by the number of foods and food forms involved with each event, the duration of the eating event can be inferred. For example a snack event involving few foods and food forms can be reasonably assigned a duration of 10 minutes. For a major meal event, the eating occasion can be assigned a duration of 20 or 30 minutes. As a result, each eating event can be assigned to 1, 2, or 3 10-minute time steps.

CSFII records do not record the order of the consumption of the foods involved in the eating event or the time that each item is consumed. It is reasonable to assume that foods are not eaten sequentially but rather in a pattern that is consistent with personnel preference. We consider this to be a random pattern of eating food items within the eating event over the time steps assigned for each eating event.

The activity patterns in NHAPS[6] are defined in terms of single minutes; however, the precision of the survey instrument and accuracy at that level of detail are questionable. It is widely recognized that survey diaries can only capture the gross temporal patterns of activities and locations particularly when an adult fills out the diary for a child (Elgethun et al. 2003). Minute-by-minute precision for parameters such as a location and activity are feasible with the survey instruments employed in such surveys. Error increases with the decrease in the size of the time step when these data are used.

Based on reasonable inference from CSFII, LLG believes that it is not advisable to develop time steps shorter than 10 minutes for the exposure models. The limitations in the definition of the duration of meals, the uncertainty in the order of the consumption of food items and the known limitations of 24 hour recall diaries make estimation of shorter time frames highly uncertain.

Reconcile the Temporal Information Structures for Dietary and Non Dietary Activities

As presented in the previous discussions and discussed in detail in the LifeLine™ Software Technical Manual, the exposure event characteristics for a simulated individual are drawn from databases such as the CSFII, NHAPS and others. Thus, for a given simulated individual, the exposure information will be drawn from records on individuals that have the same key characteristics of the simulated individual. While the records are derived from similar individuals, they still remain records from different individuals. As a result, there is a potential for a disagreement in the hourly data in these records. For example, the dietary exposure data (taken from the CSFII record) may indicate an eating event at the same time as the NHAPS indicates the child is napping.

Previous assessments calculated daily aggregate and cumulative exposures. Such estimates were not seriously impacted by this contradiction since the total daily dietary and non-dietary exposures were not affected by the exact time of the exposure event. However, when the goal is to calculate the cumulative exposure over a 10-minute period, these chronological differences must be reconciled.

[6] Data from NHAPS has been combined with other survey data to form the Consolidated Human Activity Database (CHAD). The revised version of LifeLine™ should consider using this larger database; however, the data from CHAD suffers from the same lack of precision as NHAPS.

There are a number of ways to handle this problem. For example, the eating events can be given precedence over the activities in the NHAPS records. In this case, preference for the time spent eating meals or snacks in the time step records would be given to the CSFII schedule. A second longer term option is to move the assessment to databases that contain both dietary and non-dietary activity information, such as the recent (2001-2002) National Health and Nutrition Evaluation Survey and the Department of Health and Human Service-US Department of Agriculture's Dietary Survey Integration. Other options are also possible.

The selection of the final approach will depend on a number of considerations. That discussion and this particular operation is not the subject of this report but will need to be addressed prior to the development of the revised software.

i. Proposed Approach

LifeLine™ will be modified to allow the user to define the populations to be simulated, the duration of the exposure history (from 8 hours to one year) and the duration of the time step from 10 minutes to 24 hours. The user can specify that separate exposure histories be modeled for one individual at different ages. Once this information is entered, the model will begin the first exposure history for an individual. Figure 3 presents a flow chart explaining the process of modeling an individual's exposure history.

The process starts by defining the individual's characteristics (age, gender and other factors). Based on these characteristics the model pulls the CSFII and NHAPS records for the period of time covered by the exposure history. In the case of N- methyl carbamate pesticides where the duration of the exposure histories is 24 hours, only one CSFII and one NHAPS record will be pulled. These records are then converted into a series of time step-specific records. Each record is assigned a specific start and end time. If the duration of the time step that is selected is 10 minutes there will be 144 time steps created. The record will define the microenvironment and activity for that time step and the foods consumed during that period[7]. When producing these records, the software will reconcile any conflicts between the eating event times, activities and microenvironment locations.

As part of this process, the drinking water consumption will be assigned to various time steps. The CSFII record does not record the time of drinking water consumption. However, it does indicate the source of the water. Water that is consumed as part of a food can be assigned to one or more of the eating events.

[7] The individual will be assumed to spend all 10 minutes in one microenvironment performing one macro activity. If the duration of the time set is longer than 10 minutes then the individual will be assigned multiple activities and microenvironments.

Other water consumption can be assigned as occurring over the course of the day.

Once the time step specific records are created, LifeLine™ selects the first time step record in the individual's exposure history and uses the information on the foods consumed, the location (microenvironment) and activity to determine the route specific exposures for each pesticide. The model then cycles through each of the time steps using the *Time Step Loop*.

The exposures to the pesticides that are presented at each time step are saved as a series of exposures and are linked to the times when they occurred. The data are saved and eventually exported to the PBPK/PD models as the individual's exposure history.

LifeLine™ models individuals' entire lifetimes. If there is a need to investigate exposures that occur across age ranges (<1, 1-2, 3-5, etc), the software will create an exposure history for an individual at one age, then model the individual's growth and when the individual reaches the next age range of interest, model an additional exposure history for that age range. In this way, multiple sets of age specific exposure histories for a population can be created in one model run. This process is performed in the *Exposure History Loop*.

5 c. Modeling Multiple Pesticides

One of the requirements for the cumulative assessment is the ability to model concurrent exposures from different pesticides within the family of pesticides in the cumulative exposure assessment. Up to this time, neither LifeLine™ nor any other pesticide exposure model has attempted to model the concurrent exposures of multiple pesticides. Moving from a model of an exposure assessment for a single pesticide to an exposure assessment model of multiple pesticides introduces three new requirements.

1. The first is obtaining data that accounts for the correlation between the occurrences of multiple pesticide residues in the exposure sources (i.e., co-occurrence of multiple pesticide residues on the same apple).

2. The second is the modification of the software to separately calculate and track the route specific exposures for each of the pesticides.

3. The third task requirement is the management of the increased number of outputs generated.

i. Considerations of Residue Data Appropriate for Use in Modeling Concurrent Exposures of Multiple Pesticides

Residue Data for Food and Drinking Water Sources

As discussed in the Agency's assessment of OP pesticides, the collection of residue data cannot be based on independent studies for each pesticide (EPA, 2002c). The probability of occurrence of a given pesticide and the magnitude of that pesticide on a crop commodity is correlated to the co-occurrence of residues of other pesticides on that same crop commodity. Since pesticide use in agriculture is related to seasonal pest pressures, crop treatment traditions,

employment of competitive pest control methods and pesticide cost factors (as well as other market-related factors), occurrence of multiple pesticide residues on given crop commodities are related in terms of probability of occurrence and in terms of magnitude of the residues.

In the current versions of LifeLine ™ software, residue distributions can be applied either at the crop level or to the CSFII food level. Residue data relevant to the crop commodities are applied to the crop level interface along with relevant processing factor information. Residue data relevant to the foods as eaten can be applied to a listing of foods utilized in the food consumption database.

One solution is to rely on contemporary survey data where every pesticide included in a cumulative risk assessment is measured concurrently in a sample of a RAC. Such surveys capture the correlations between the residues. In the OP cumulative dietary risk assessment EPA used residue monitoring data collected by the United States Department of Agriculture's Pesticide Data Program (USDA-PDP) supplemented with information from the Food and Drug Administration Center for Food Safety and Applied Nutrition (FDA/CFSAN) monitoring data (EPA, 2002c). For drinking water, data on concurrent residue levels of pesticides data were derived using regional use data and the PRZM and EXAMS models. These types of data are expected to be used for the assessment of N-methyl carbamate pesticides.

It should be recognized that this approach, using survey data, is limited to retrospective assessments with contemporary data applicable to all commodities involved in the risk assessment, wherein all uses of registered pesticides within the family have been included in the assays. This approach cannot be used for the prospective evaluation of new pesticides and modification of use patterns for existing registered products for which EPA considers registration and tolerance setting. Challenges for the regulator include situations when there is a paucity of acceptable monitoring data, when the data are not contemporary or where not all crop uses are accounted for in the residue survey data.

Use of the Model for Prospective Evaluation of New and Existing Registered Products

Databases exist which detail the co-occurrence of multiple pesticides on foods, water and other media that may provide opportunities for simultaneous exposure to humans during a single time interval. The residues from specific pesticides as well as the co-occurrence probability are in many instances a part of these databases or can be derived from the databases. There are multiple ways to assign these residue values to the exposure assessment parameters. Some approaches may yield an underestimation of the true exposure; some may yield an overestimation of the true exposure. Scenarios which must be considered when choosing residue data for the analysis input (for multiple pesticide cumulative exposure assessment) include:

1. Registrant makes a claim of reduced risk.
   Issue: Is the risk profile actually reduced for the resulting cumulative risk assessment when the new cumulative residue profile is constructed?

2. A new product is coming onto the market.
   Issue: What are the displacement curves in the cumulative residue profile for the new product and existing products for the same uses?

3. Regulatory action is taken to cancel one or more pesticides in a family of pesticides.
   Issue: since the pest pressure remains, how do the remaining pesticides fill the void and what is the resulting cumulative exposure assessment?

4. Some crops within the pesticide/crop matrices are imported during key seasons. Issues: What is the seasonality of the residue profiles and how are the differences between pesticide use practices in the US versus those in the exporting countries taken into consideration?

Since the residue profile (occurrence and magnitude of use) for any one pesticide is correlated with the residue profiles of other co-occurring pesticides registered for similar uses, one cannot simply add a new pesticide profile into an existing residue survey. Likewise, one cannot simply extract a particular pesticide profile from the residue survey with an array of pesticide residues. Addition or removal of a pesticide or some of its uses from commerce can result in changes in the market share of the remaining pesticides in the group. These changes may partially or completely compensate for the loss of the extracted pesticide.

In the cumulative assessment for N-methyl carbamate pesticides, each pesticide's exposure profile will be maintained separately. Because of this requirement, the organization of the residue data will require a different and more complex structure than earlier single pesticide assessments. In single pesticide assessments, data on residues are entered on the commodity or food form level

using an input table. In cumulative assessments, the data will be entered in a manner that maintains a link between the specific residue levels that occurred in a specific sample from the survey, thus preserving the information on co-occurrence.

An approach that achieves this goal is a two dimensional array that lists each residue of the pesticides in the individual samples in the database. Table 1 presents an example of how such data can be organized in the input files for the dietary simulation. In this example, there are 10 residue values for carrots for each of six co-occurring pesticides. This structure will be repeated for each of the commodities in the residue database.

Table 1. Example of the Structure of Residue Data for One Commodity: Carrots

Crop Group		Commodity			Samples									
Code	Name	Code	Name	Pesticide	1	2	3	4	5	6	7	8	9	10
1	Root And Tuber Vegetables	780	Carrot	Pesticide A	0.0001	0.0001	0.002	0.0001	**0.005**	0.0001	0.005	0.002	0.0001	0.005
1	Root And Tuber Vegetables	780	Carrot	Pesticide B	0.0001	0.0003	0.0001	0.0007	**0.0001**	0.0007	0.0001	0.0001	0.0007	0.0001
1	Root And Tuber Vegetables	780	Carrot	Pesticide C	0.0001	0.0001	0.0034	0.0001	**0.0001**	0.0001	0.0001	0.0034	0.0001	0.0001
1	Root And Tuber Vegetables	780	Carrot	Pesticide D	0.0001	0.002	0.0001	0.0002	**0.0004**	0.0002	0.0004	0.0001	0.0002	0.0004
1	Root And Tuber Vegetables	780	Carrot	Pesticide E	0.0001	0.0001	0.002	0.0001	**0.0001**	0.0001	0.0001	0.002	0.0001	0.0001
1	Root And Tuber Vegetables	780	Carrot	Pesticide F	0.002	0.002	0.002	0.002	**0.002**	0.002	0.002	0.002	0.002	0.002

Using this structure, the dietary software will select a “column of data” for a single sample, such as column 5 in the above table. Values in this column will be used to represent each pesticide’s residue in a food containing carrots, as the possible residues in CSFII foods are calculated. In the simplest case of eating a raw carrot, the dietary exposures from the six pesticides would be equal to the amount of carrot consumed times each of the respective six residue levels. This data format can also apply to blended commodity scenarios, where the mean value of each pesticide would be calculated (mean of each row) to represent the pesticides’ residue values. This is in keeping with the EPA policy for dealing with blended commodities.

Since the database of residues is at the commodity level, the raw data will not reflect the residues at the “Food Form” level. To define the residues at the food form level, the user will have to modify each of the pesticides to reflect how the residues are likely to change with processing. This modification could be accomplished by entering the data at the food form level or by using an expanded set of processing factors within the LifeLine™ Food Residue Translator. Details on this program module are given in the Technical Manual.

Data for Residential Assessment

The residential exposure assessment must also deal with the issues of correlation of residues for multiple co-occurring pesticides. Residue profiles (occurrence probability and magnitude) of different pesticides in an individual's home are correlated because of homeowner pest management practices. If homeowners control a pest by using a single product, they are not likely to then use a second competing product. As a result, the presence of residues of competing products is expected to be negatively correlated. In other scenarios where homeowners could be anticipated to use multiple products (a flea bomb for a home, a spray for pet bedding and a collar for the pet) certain products may be positively correlated.

The pesticide exposure profiles experienced by an individual also may be correlated over time. If a pesticide is used in a home on one day, the residues will persist over time. Further, a single product (large spray can) may be applied multiple times in a season to control pests. Thus, use of a specific product in a home on one day may imply repeated exposures to the same pesticide over time rather than exposures to competing pesticide products.

In the LifeLine™ software, residential exposure assessments are based on data on pesticide use and studies of the exposure that will occur if a product containing the pesticide is used. The probability of using a pesticide was modeled by decomposing the process into two steps. First, what is the probability of needing to control a pest, and then given that a person is controlling a pest, what is the probability of using a product containing a specific pesticide?

Data are available on the first step of this process in the form of surveys of "pest pressure". Pest pressure is defined as the frequency that a specific pest (insect, weed, fungus, etc.) is treated in a specific microenvironment in the home or yard. Data on pest pressure are taken from the 1991 National Home and Garden Pesticide Use Survey (NHGPUS) (RTI, 1991). Because pest pressure is a function of the climate and housing stock, data on the need to control pests is believed to be somewhat stable over time. Pesticide product market shares are much more variable as pesticides come on and off the market, as alternative methods are employed and as pesticide product prices change. Use of contemporary market share data, when available, allows EPA to model contemporary pesticide usage in lieu of new use surveys.

Under this approach, LifeLine™ models the times that the homeowner treats a pest in a specific microenvironment. This modeling is performed by selecting a record from NHGPUS and taking the number of treatments to generate a daily application frequency that is applied to the appropriate seasons when the pests will require controls. Each instance where a pesticide is applied is assumed to be a single pesticide product. In addition, the model assumes that for any given

year, a pest in an individual's home is treated using products containing the same active ingredients (LLG, 2004).

This "pest pressure" approach allows the simulation of exposure to multiple pest products containing multiple pesticides. Since each application is linked to a specific product and pesticide, the residential exposures can be linked to the individual pesticides.

This approach only requires the user to identify the market share of each of the N-methyl carbamate pesticides used for controlling a specific pest. Therefore, the approach is amenable to both retrospective analyses and for the evaluation of new products and their impact on cumulative risk.

ii. Modification of LifeLine™ to Separately Calculate, Track, and Save Exposure Information for Multiple Pesticides

LifeLine™ software was designed from its inception to support assessments of cumulative risk (LLG, 1999, LLG 2002). The design of the software uses a series of nested loops to model the concurrent operational aspects of exposure calculations. As Figure 2 indicates, the dietary exposure estimation process for a single day and a single pesticide uses a loop (the Dietary Exposure Event Loop) to cycle through each food (and drinking water) in a CSFII record. In each of these loops, the dietary exposure from consuming the food and drinking water is determined based on the amount of food consumed and the residues in the foods. As indicated in Figure 4, adding a new loop, *The Pesticide Loop*, allows the software to separately determine and track the exposures from each pesticide in the family of pesticides in a cumulative assessment.

Continuing with the dietary example, in the new *Time Step Loop*, the software will select a dietary record and then cycle through each of the foods consumed within the time step using the *Exposure Event Loop Diet.* For each food in an eating event within the time step, the model will survey the residue data structure to determine if the first pesticide in the cumulative assessment is present. If the residue is present, the exposure resulting from that residue (for just that pesticide) is calculated and saved. This is repeated for each pesticide. Then the model returns to the *Exposure Event Loop Diet* and moves to the next food. Once all of the foods are evaluated, the data for the exposure of a pesticide from each food are summed for the time step to give the total dietary exposure of that pesticide for that time step. This is repeated for all of the pesticides within the family of pesticides. The result is a record of the total dietary exposure for each pesticide within the time step where each pesticide-specific exposure value is correlated to the others within that time step.

A similar approach is used for drinking water and for the residential exposure assessment. As shown in Figure 4, a new loop, the *Pesticide Loo*p, is added to the non-dietary, non-occupational exposure assessment portion of LifeLine™.

This loop will be trigged when a new microenvironment is considered and exposures associated to residues in that microenvironment are calculated. The software cycles through the loop to separately determine if each pesticide is present, and what exposure would result if it were present. Unlike the dietary portion of LifeLine™, which only addressed oral exposure, this loop will separately calculate the three possible routes of exposure (oral, dermal and inhalation). The exposures for each pesticide that occurs by a given route from all of the microenvironments during a time step are then summed to yield the route-specific total residential exposure for that pesticide. This process is performed separately for each pesticide within the family of pesticides and each pesticide-specific exposure value is thus correlated to the others within that time step.

5 d. Matching the LifeLine™ Exposure Outputs to the Definitions of Dose in the PBPK/PD Model

As discussed in the earlier sections the process of a pesticide moving from an environment to the target organ or compartment of the exposed individual is a multi step process (EPA, 1992; EPA, 1997). It is critical that the output of the exposure model defines exposure and/or dose in terms that are consistent with the definitions used by the PBPK/PD model. The exposure assessment model must deliver exposure metrics at the exact point on the continuum where the PBPK/PD risk assessment model commences. There can be no gap (such as not accounting for the factors involved as the pesticide moves through the dermis), nor can such elements be represented in both models yielding duplicative calculations for the element.

Some PBPK/PD models define doses in terms of the dosing protocols used in toxicology studies on which dose-effect associations are modeled. Examples of this are the values representing the airborne level of the pesticide in an inhalation chamber in a toxicology study or the concentration of pesticide in the test animal's diet. These media-specific concentrations may be held constant over the duration of the experiment and can be described by a single value and a clearly defined duration. This profile of exposure is unlikely to represent the human experience of exposures to pesticides in real life, where the air concentrations vary from moment to moment and dietary exposure changes with every eating occasion every day. As a result, the dose metrics produced by the exposure model for the PBPK/PD model require a slightly different approach from traditional exposure assessment outputs. The following sections present the proposed approach for each route of exposure in the exposure model supporting the PBPK/PD risk assessment models.

i. Oral Exposures

Oral exposures result from three sources in LifeLine™: food, drinking water and incidental hand to mouth contact. Each food item has a different residue level. The number of consumed foods, type of eating occasion and amount of each food item consumed are defined for each time step. Consumption of the food items is considered to be randomly distributed across the time step(s) in which the eating occasion occurs and occupies the full duration of the time step(s) associated with that eating occasion. A more detailed discussion of this process is provided in the previous section of this document. As a result, the oral exposure from diet is defined as a mass intake for the time step:

$$D_i = \Sigma \; F_{ij} \, A_j \; / \; S$$

Where D_i is the exposure of the i^{th} pesticide, F_{ij} is the concentration of the residue of the i^{th} pesticide in the j^{th} food, Aj is the amount of the j^{th} food consumed in the eating occasion and S is the number of contiguous time steps over which the eating occasion occurs.

If S is two or three, the paradigm assumes eating occasions occupy 10, 20 or 30 minutes, D_i will be the same for the next one or two time steps. A similar approach will be used for the consumption of drinking water determined to occur during an eating event.

Oral exposure from hand to mouth events will be modeled based on the assumption that the exposure continues at roughly a constant rate while an individual is in a microenvironment performing an activity. The exposure will be defined as the amount of pesticide that is removed from the hand by hand to mouth contact.

ii. Dermal Exposures

Dermal exposure to pesticides occurs from three sources: dermal contact with pesticide residues on contaminated surfaces; dermal exposure to the product during application; and from showering with water containing pesticides. The exposures for showering are different from the other two types of exposure and require a different measure of exposure. In the case of showering, the majority of the body is in contact with essentially an infinite source (pesticide in water that is constantly flowing over the skin.) In the showering scenario, dermal exposure will be defined in terms of the concentration in water and the duration of contact.

In the case of dermal exposure to residues on surfaces and dermal exposure during pesticide application, a finite amount of pesticide deposits on the skin and remains there until it is absorbed or is removed by some process.

In the applicator and post application scenarios, the amount of a pesticide on an individual's skin and the area over which this exposure occurs will be modeled over time. In the case of the applicator exposures, the "unit" exposure rate and the duration of the application event will be used to determine the loading rates and the area exposed for each time step. In the case of the post application exposures, the dermal transfer rates, clothing and duration of time spent in the microenvironment will be used to define the loading rate for each time step. Residues are assumed to remain on the skin until removed by dermal absorption, bathing, hand washing or hand to mouth contact. For bathing and hand washing, a washing removal efficiency is used. This approach has been used in the SHEDS model of dermal exposure (EPA, 2002c).

In this approach, there will be an estimate of the average amount of pesticide present on the skin and the area of skin that is contaminated for each time step. The model does have the capacity to estimate other exposure parameters i.e. delivered dose, as the PBPK/PD model requires.

iii. Inhalation Exposures

Inhalation exposure occurs during showering, during pesticide application, and during post application activities. Exposures for all three inhalation scenarios will be defined in terms of the mass of pesticide inspired in a time step. If the exposures from inhalation scenarios are critical to an assessment, it may be necessary to determine what fraction of the inspired exposure:

- Reaches the deep lung and is absorbed:
- Impacts the nasal pharyngeal region and bronchial tubes and should be addressed as an oral exposure;
- Is absorbed in nasal pharyngeal region and bronchial region; or
- Is exhaled unchanged.

iv. Summary

In summary, the route specific exposure information provided to the PBPK/PD model will consist of:

- The mass of each pesticide ingested in a time step from drinking water, from food and from incidental hand to mouth contact;
- The mass of each pesticide inspired in a time step;
- The average mass of pesticide on the skin and the area over which the exposure occurs for each time step; and
- The concentration of pesticides in shower water and the whether or not showering occurs in a time step.

This information will be provided for each pesticide, for each time step, for each individual simulated and concurrent metrics will remain linked.

5 e. Modeling Physiological and Genetic Variability in Partitioning, Metabolism, and Dose-Effect Relationships in PBPK/PD Models

As discussed above, for the LifeLine™ software to define the contact doses received by an individual, the software must define the characteristics of the individual receiving the doses. This definition of the individual provides a framework for defining or assisting in the definition of many of the parameters for the PBPK/PD model. The PBPK/PD cumulative risk assessment model will deal with such issues such as distribution of the pesticide from routes of exposure to various target organs, partitioning of the pesticide from blood to the target tissues, metabolism and the quantitative dose-effect relationship at the molecular or clinical level. Given that many of these parameters may be influenced by

interindividual differences related to age, gender, ethnicity, activity level or other characteristics defined in the LifeLine™ exposure assessment model, those definitions should be linked to the exposure data for each individual (applied at the appropriate level of detail in the exposure history). The authors of the PBPK/PD model must describe the way in which this information is employed within the risk assessment model.

i. The Lifeline™ Framework

The current version of the Lifeline™ software assigns a number of characteristics to each individual in a simulation. The process used to perform this is described in detail in the Lifeline™ Technical Manual (LifeLine™, 2004). The following is a brief summary of the process.

The process begins by assigning characteristics to an individual at birth and modeling how the characteristics vary over time (Figure 5). LifeLine™ begins by assigning an individual a gender, race, and ethnicity. Based in these fixed characteristics, the software assigns a body length to each individual for the first year of life. Data on race and gender specific growth in height is then used to model height changes over the individual's life.

The result is an estimate of the individual's height at each year of their life. These age-specific heights are then used to select the body weights for those ages. The equations used for modeling are based on data taken from NHANES III. Knowing the age, height and weight of the individual allows the determination of the surface area of the hands and whole body.

In addition, once the height and weight of the individual are known, the body mass index (BMI) can be determined. The BMI can, along with age and gender, be used to predict the resting breathing rates. These resting breathing rates can be used along with information on the level of activity to determine the breathing rates under various levels of activity. LifeLine™ determines breathing rates for resting and sleeping, sedentary activities and three levels of active behavior (light, moderate and heavy). The result of this process is a determination in Lifeline™ Version 2.1 of the following physiological criteria of each individual in a simulation:

- Demographics:
  - Race
  - Ethnicity
  - Gender
  - Age
- Physiology
  - Height
  - Weight
  - Body Mass Index (BMI)
  - Surface area
    - Whole body
    - Hands
  - Breathing rates
    - Resting and sleeping
    - Sedentary activities
    - Light activities
    - Moderate activities
    - Heavy activities

ii. Proposed Modifications

P^3M

While the current version of LifeLine™ provides an excellent basis for developing the inputs for PBPK/PD modeling, the proposed modification of this framework draws upon a related project accomplished by the LLG scientists[8]. In that project, a software program Physiological Parameters for Physiologically based Pharmacokinetic Models (PPPM or P^3M) was created. P^3M was developed to produce demographically specific and internally consistent values of the physiological parameters (Price et al. 2003b). P^3M was created based on published studies that reported correlations between various physiological

[8] The described software, P^3M is copyrighted protected and distributed via LINEA, Inc. The software is available to the public without fee via the LINEA web site: www.lineainc.com. Authors have granted exclusive license for its use in the LifeLine™ model as proposed in this document.

parameters and individuals' height, weight, gender, age and ethnicity. Based on that review empirical models were identified that allowed the prediction of correlated volumes of many compartments, tissues and organs. The specific algorithms vary with the tissue under consideration, but generally consist of a series of regression models for various ages and genders. These algorithms captured the bulk of the inter-individual variation.

An example of the approach used in P3M is given below. In this example, a model (here a set of equations) is developed for predicting kidney volume and blood flows:

Adults (Males and Females)

Total Weight of Kidneys (g) = 15.4 +2.04*BW + 51.8*BH (m) ^{2} (R^2= 0.64)
(Kasiske and Umen 1986)

Children Male and Females:

Left Kidney Volume (ml) = 4.214 * BW (kg) $^{0.823}$ (R^2= 0.97)
Right Kidney Volume (ml) = 4.456 * BW (kg) $^{0.795}$ (R^2=0.97)
(Dinkel et al. 1985)

Additional information on the model is contained in the manuscript "Modeling Inter-individual Variation in Physiological Factors Used in PBPK Models of Humans" presented in Appendix A of this document.

As part of the P^3M project, the resting blood flow for each organ was also calculated based on estimated volume of the tissues and literature values of tissue specific blood flow rates. The data for kidneys are as follows:

Tissue blood flow:
Males 3.68 (l of blood /min/l of tissue)
Females 3.22 (l of blood /min/l of tissue)
(Williams and Legett, 1989)

Thus the blood flow in l/m for a male child would be:

= (4.214 * BW (kg) $^{0.823}$ + 4.456 * BW (kg) $^{0.795}$)/1000* 3.68 (l of blood /min/l of tissue)

The organ and tissue-specific calculations from each of the algorithms can be summed to give estimates of the commonly used PBPK/PD compartments (well perfused, poorly perfused and fatty tissues) for each individual. Finally, the blood

flows for all of the organs can be summed to provide an estimate of the total resting cardiac output[9].

Estimates of volume and blood flow are available for the following organs, organ systems, tissues, and compartments:

1. Total well perfused tissues
2. Red marrow
3. Lungs (tissue volume)
4. Brain
5. Kidneys
6. Liver
7. Pancreas
8. Thyroid
9. Spleen
10. GI organs (total tissue volume for stomach and small and large intestines)
11. Blood
12. Plasma
13. Blood cells
14. Total poorly perfused tissues
15. Dermis
16. Epidermis
17. Skeletal muscle
18. Heart (Tissue volume)
19. Tongue
20. Total fatty tissues
21. Adipose issue
22. Yellow marrow
23. Bone tissue

Proposed Approach

Based upon the empirical models developed in the P^3M project and the characteristics currently assigned to individuals in the LifeLine™ Software, the volumes and resting blood flows of the above tissues and organs can be specified for every individual at every age in their lives.

The P^3M project also developed models of the resting breathing rates and cardiac output. The resting breathing rates are based on the work by Layton (1993). The PBPK/PD model being developed by ORD/EPA for the cumulative risk assessment uses the alveolar ventilation rate rather than the breathing rate (minute volume). To convert from the breathing rate to the alveolar ventilation rate a correction is necessary to account for the physiologic dead space volume.

[9] Note the actual process of deriving the blood flows for the well-perfused tissues and for the total cardiac output has to be corrected for organs and organ systems where the blood flow occurs in sequence (GI and the liver).

EPA (1996) reports that the alveolar ventilation rate is 70% of the breathing rates. However, it may also be possible to predict alveolar ventilation rates based on alternative models (Neder et al., 2003**;** Bennett and Zeman, 2004; and Harris 1978).

The PBPK/PD model being developed by ORD/EPA for the cumulative risk assessment is expected to describe blood flow using two types of data, the total cardiac output and the percentage of the cardiac output that goes to each compartment. The proposed approach will directly provide the total cardiac output. The percentage going to each compartment can be estimated based on the compartment specific flow rates and the total cardiac output.

Providing Information Relevant to Interindividual Variation for PBPK/PD Model Elements

Parameters such as partitioning, metabolic factors and dose-effect relationships can vary across individuals. Some of this variation may be related to the physiology, gender or age of the individuals. In addition, a great deal of research is being performed on the genetic contribution to this inter-individual variation. To the extent that the factors can be related to the any of the demographic information (age, gender, or race) or physiology (body type) these factors can also be modeled. Because of this potential opportunity, the proposed LifeLine™ outputs to the PBPK/PD model will include demographic information associated to the calculated exposure values.

Modeling Time-Dependent Physiological Parameters

The volume of the various organs, tissue and compartments do not vary significantly over the course of a few hours or days. Thus, the values for these parameters are assumed constant over these short time periods. However, blood flow and the alveolar ventilation rates are not constant and vary with the individuals' activities. Activities that are more strenuous will raise both the cardiac output and the alveolar ventilation rate and will change the fractions of the cardiac output going to different organs. Consumption of food will change the fraction of cardiac output going to the digestive organs.

This time-dependent and activity-dependent variation can be captured by estimating values for these parameters for each time step of the exposure history. As discussed in the prior section of this report, the duration of the time steps can range from 10 minutes to 24 hours. The duration of time over which these values can be modeled (the exposure history) can be as short as 24 hours or as long as 365 days.

One approach for estimating the impact of activity on values for breathing rates and blood flow is to employ estimates of changes in breathing rates to estimate the impact on cardiac output. Layton (1993) proposed a simple set of factors for

various levels of activity that are multiplied by the resting breathing rate to yield breathing rates associated with various levels of exertion. In LifeLine™ software, these factors are linked to the various activities listed in the activity patterns and are used to define the average breathing rate for an individual's macro behaviors over the course of a day. Using this approach, it is feasible to estimate the breathing rates for each 10-minute time step in an exposure history.

The breathing rates can be linked to alveolar ventilation rates and these can in turn be used to predict the corresponding cardiac outputs. The cardiac output in the current PBPK/PD model is estimated based on the alveolar ventilation rate using the equation

$$CO = A0*QA0 + A1 (QA - QA0)$$

where

A0 is the ratio of the cardiac output to alveolar ventilation rate under resting conditions;
A1 = the fractional increase in cardiac output for an increase of the alveolar ventilation rate;
CO = Cardiac output for a given level of activity;
QA = Alveolar ventilation rate for the level of activity; and
QA0 = Alveolar ventilation rate under resting conditions.

Using this approach, it will be possible to define the cardiac output and alveolar ventilation rate for each 10 minute time step of an individual's exposure history.

Finally, since LifeLine™ includes a detailed time-related profile of food consumption, the model can calculate eating-related temporal changes of cardiac output and the changes for percentage of cardiac output for each compartment of the PBPK/PD model. This can be presented for time steps that include an eating occasion and for time steps that follow a time step containing an eating occasion.

In summary, the current approach used in LifeLine™ software can be extended to address both the time dependent and time independent physiology parameters required by PBPK/PD models.

5 f. *Designing the Interface between LifeLine™ Exposure Model and the PBPK/PD Model of Cumulative Risks*

Once the modifications are made to the current LifeLine™ exposure software, there remains the conceptually simple but technically challenging task of linking the information from LifeLine™ to the PBPK/PD model. There are two basic approaches to accomplish this. One is the integration of the two models into one;

the second is the creation of an interface to deliver a properly formatted data file from the exposure model to the PBPK/PD model.

An advantage of integrating LifeLine™ and the PBPK/PD model is that the resulting merged model would preserve a perfect continuum of algorithms beginning with the various exposure events and progressing to the target tissue dose-effect calculations for each time step in the simulation. There would be a seamless interface between the output metrics from the exposure model and the input requirements of the PBPK/PD model. It would also assure correct calculation of the exposure source contributions for any specific target tissue dose-effect values.

However, there are strong advantages to preserving the independence of these two models and creating a flexible and responsive interface between them. This approach recognizes the fact that the exposure assessment model is a relatively advanced tool that has evolved over the years. It functions on a fast operating system which can process great numbers of calculations and store a giant block of answers for convenient viewing options. As technology has advanced, so too have the operational options and available functions of the exposure model. By comparison, PBPK/PD models such as the EPA/ORD ERDEM (Exposure Related Dose Estimation Model) model are not yet as advanced. This may also be the case for other PBPK/PD models. The model architects have focused on basic construction elements and design concepts. Building fast operating systems are not yet the priority issue, and even the design elements will likely change as experience grows with these developing models. Another important reason to maintain separation of the two model types is that it permits both models to evolve with their respective science and technology and avoids some of the resource (time and financial) issues intrinsic to the integrated model.

The key to success in pursing the approach of two separate models is to develop a flexible and reliable interface or ‘bridge” between the exposure model and the PBPK/PD model— one that has the capacity to evolve as new versions of PBPK/PD models are developed. This interface is most logically built to receive output data from the exposure model and to modulate it to mesh with the input requirements of the PBPK/PD model. It must also take into consideration the technical realities of the PBPK/PD models of today, and the likelihood that their capacity to receive more data i.e. the “delivered data load” will increase as the models evolve.

5 g. Processing Demands

To design this interface, it is helpful to consider key factors imposed by the flanking models and the user for whom it is being built. The following figure summarizes the factors raised earlier in this document (Figure 6).

In a matter of minutes or hours of computational time, the LifeLine™ model can deliver an immense block of exposure profiles that quantify the source specific/route specific exposures for 100,000 individuals along with each individual's demographic, physiological and anatomical information, as described in this document. In the coming years, it is expected that the model will yield even more information bits as the time steps for these exposure assessments become smaller and as other functions are incorporated. The model can express its answers as exposure to the individual or as absorbed dose by given routes.

The PBPK/PD model is newly developed and, as with most new models, operates on a relatively limited system, which may have significant data volume and operational speed limitations. Yet, the PBPK/PD model demands great detail for the exposure metrics (small time steps, route specific exposure, etc) linked to all details about the exposed individual. Thus, no compromise can be made on the option of delivering as much
information as possible on the individual and on that individual's exposure profile for the chemical(s) in question. The PBPK/PD model is likely to change significantly as it is developed; as scientists accrue operational experience with it, and as it address different chemicals with different needs vis-à-vis the physiological metrics of importance. This evolution could be quite rapid and other models may emerge as well.

The user—EPA's Office of Pesticide Programs—needs a tool that expresses the exposure and risk profiles in a way that reflects their regulatory needs. Traditionally, the risk-

Figure 6. Proposed Linkage of Lifeline to PBPK/PD Model

based regulatory issues have focused on scenarios dealing with “highest exposures” and “sensitive sub populations” and route-specific risk. Although a full view of the distribution of risk across populations is valuable to public health professionals and researchers, that view may have limited value for the decisions mandated under FIFRA, FFDCA and FQPA. The focus of the risk assessment is driven by the legislation and EPA/OPP policy. The filter can accommodate whatever part of the distribution of exposure across the population that EPA needs to focus on. (See Figure 7).

Thus, the interface must be able to:

- Characterize and deliver a defined population that is sufficiently small to be run in the PBPK/PB model but large enough to represent the target population for which exposure profiles are desired.
    - Ideally, the user should be able to select the points on the distribution and the subpopulations of interest to direct the filtering work of the interface. The individuals delivered to the PBPK/PD models should reflect the policy of the EPA/OPP as to their regulatory interest. Current regulatory goals are designed around risk calculations at the 95 to 99.9th percentiles of an exposed population. Definition of risk at this extreme tail in the distribution of risk values usually requires that populations of 10,000 to 100,000 individuals be simulated in the LifeLine™ model. In addition, separate assessments are made for up to nine different age and gender defined populations. Because of the limited capability of the PBPK/PD model, only a fraction of the individual exposure histories generated by LifeLine™ could be transferred the PBPK/PD model for derivation of the risk assessments.

    - The interface must filter the information and deliver an appropriate data density in the right format for the PBPK/PD model. This is a technical detail, but very important. Thus, LifeLine™ output through the interface should deliver files that are easy to import into the PBPK/PD model(s), easy to rearrange and manage. Obscure file structures would be detrimental to this critical requirement. These parameters are likely to change as the PBPK/PD models become more sophisticated and run on faster operating systems. The interface should respond to such upgrades by permitting more information to flow (less filtering) at the user's command.

- Convey the demographic and physiological parameters that do not vary with time (during an individual's exposure history) for the simulated individuals; and

- Convey the time variant information on exposure and activity-dependent physiological parameters. The requirements for these may vary from one chemical class to another as different mechanisms of action at different tissue sites are involved. Ideally, the user could specify which parameters are of interest, allowing the interface to filter out unnecessary data elements for the PBPK/PD model.

Figure 7. Options for Selecting Records for PBPK/PD Analysis

Finally, the interface from the exposure model to the PBPK/PD model must be fashioned whereby the information is transferred without losing the interconnections of multiple pesticide, multiple route exposure values for a coherent series of time steps for each individual with the relevant physiological and demographic identifiers. The interface must faithfully maintain the continuum from the media concentration values to the target tissue doses without creating gaps or overlaps, as previously discussed

The proposed approach will be to revise LifeLine™ to allow the analyst to customize the exposure outputs for the specific PBPK/PD analysis to be run. The analyst may choose the desired target tissue calculations from a menu consisting

of the 23 tissues, organs and compartments listed above. The analyst will then define the duration of the time step 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.

An example of the way in which the interface could work is presented below. In this example, it is assumed that EPA would be interested in the upper percentiles of the exposure distribution for its regulatory inquiry and would thus select exposure profiles for those individuals within the population with the highest exposures. The vast bulk of the LifeLine™ data block would thus be filtered out and left behind.

The process of selecting the records to deliver to the PBPK/PD model requires special attention and a transparent prioritization scheme based on explicit criteria and definition of each detail of the filtering process. Those approaches could be based on any of many criteria. These criteria deserve careful consideration by EPA and when specified, can be accomplished by the LifeLine™ interface.

One example of a process for selecting records would be as follows:

1. The exposure software would create a demographic, physiological and exposure history for an individual.
2. The data would be evaluated against screening criteria that would eliminate individuals with a low potential for adverse effects.
3. If the record was found to exceed the criteria then it is included in the Access™ file that will be run in the PBPK/PD model of cumulative risk. In addition the information would be saved as part of the LifeLine™ software outputs
4. If the record were not found to exceed the screening criteria then it would not be sent on to the PBPK/PD model but would be saved as part of the LifeLine™ master output file.
5. The interface Access™ file is exported to the PBPK/PD model and the high-risk records would be run through that model. The records that are determined to have exceeded some user-defined threshold would be identified.

The findings of which records exceeded the user-defined threshold will be evaluated using the data set of all records saved by LifeLine™ to determine the factors that are associated with these.

5 h. Output File Structure

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. The first contains the data that remains constant over the exposure history. The second is a table of the time dependent information.

The time dependent information is presented as a set of values for each of the time steps in the individual's exposure history.

Table 2 presents an example of a table of time invariant information for a PBPK/PD model with five compartments. The information is divided into two areas the demographics of the individual and the compartment volumes of the individual's physiology.

Table 2. Time Independent Data								
Demographic Information				Volumes of Selected Compartments of PBPK/PD Model				
Age	Gender	Race	Ethnicity	Comp. 1	Comp. 2	Comp. 3	Comp. 4	Comp. 5

Table 3 (parts a and b) presents the time dependent data for a cumulative risk model of three pesticides. Each row presents data for a single time step. The tables present the data for the first two and the last of the 144 ten-minute time steps in a 24-hour exposure history for the individual. Table 3a presents the data necessary for determining the route specific doses of the three pesticides.

Table 3a. Time Dependent Data (Part 1)																
Time Step		Measure of Inhalation Exposure (mg)			Measure of Oral Exposure (mg)			Concentration in Shower Water (mg/l)			Measure of Dermal Exposure (mg)			Area of Dermal Exposure (cm2)		
Begin. Time	End. Time	Pest. 1	Pest. 2	Pest. 3	Pest. 1	Pest. 2	Pest. 3	Pest. 1	Pest. 2	Pest. 3	Pest. 1	Pest. 2	Pest. 3	Pest. 1	Pest. 2	Pest. 3
0:00	0:10															
0:10	0:20															
23:50	24:00															

Table 3b presents the time varying physiology of the individual for the same time steps.

Table 3b. Time Dependent Data (Part 2)								
Time Step				Fraction of Cardiac Output for Each Compartment				
Begin. Time	End. Time	Cardiac Output	Alveolar Ventilation Rate	Comp. 1	Comp. 2	Comp. 3	Comp. 4	Comp. 5
0:00	0:10							
0:10	0:20							
23:50	24:00							

This approach can also be used for linking PBPK/PD models of a single pesticide as well as multiple pesticides. In this case, data would be presented only for a single pesticide.

Obviously, the exact details of the output file will depend on the parameters selected for sending to the PBPK/PD model (as discussed above). This example demonstrates the concept for delivering such parameters in a coherent and linked fashion.

The technical aspects of the development of the interface can be achieved readily with existing techniques using the framework of the LifeLine™ exposure output files. LifeLine™'s original configuration anticipated this stage in the evolution of risk assessments, and thus its infrastructure will accommodate flexible, efficient and user-friendly portals such as this interface.

However, much attention should be given to the criteria by which the data are filtered through the interface. This is an option to be directed by EPA—almost any focus can be accomplished by the software. Thereafter, there must be complete transparency of the mechanics by which the filtering is accomplished by the interface. The filtering task of the interface yields data representing only a small fraction of the original data block. The Agency and all stakeholders should understand the nature of the data delivered to the PBPK/PD model and the nature of the data left behind and the statistical consequence of this filtering.

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Appendix A. Modeling Inter-individual Variation in Physiological Factors Used in PBPK/PD Models of Humans (Price et al. 2003b)

The PDF file for the reference of this manuscript is provided separately.