THE LIFELINE GROUP

Construction of a Comprehensive Chemical Exposure Framework Using Person Oriented Modeling

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Executive Summary

There is a growing recognition that a person's exposure to specific chemicals occurs via multiple routes from multiple sources. To adequately evaluate such exposures, the scientific community requires models that can predict the occurrence of exposures for each potential combination of pathway and source, and then accumulate these exposures over time. Ideally, such models will account for variations in people's activity patterns that are influenced by age, gender, occupation, and other demographic factors. These activity patterns should account for the movements of individuals through microenvironment that are consistent with the season of the exposure, the geographical location and the demographics of the individual.

The American Chemistry Council has funded the development of a comprehensive chemical exposure framework that would allow the construction of such models. The Framework was developed by a team of experts in the field of exposure assessment led by The LifeLine Group, Inc. a non-profit corporation created to develop tools for assessing exposures to chemicals.

This report presents the results of a multi-year effort to develop a conceptual framework for modeling multi-chemical, multi-route, and multi-source exposure (hereafter called the Framework). This Framework, while simple, has the ability to model doses from acute to lifetime doses, for periods ranging from pre-conception (maternal and paternal doses) through birth to the elderly. The approach can be extended to any number of chemicals, sources of exposure, and routes of exposure. The approach allows for the correct separation inter- and intra-individual variation and uncertainty. Finally, the proposed approach is consistent with the majority of models currently under development by regulatory agencies, academia, and industry.

The report begins with a review of existing exposure software (Chapter 2). The software programs were identified using professional contacts and a literature search. Each program is reviewed to determine the techniques and model architecture used in the model. In particular, the models were reviewed to determine how they evaluated variation in exposures across individuals, longitudinal exposures in the same individual over time, and uncertainty in the exposures.

Chapter 3 presents the Framework. The Chapter begins with the presentation of a discussion of the limitations of source-to-dose models and the concept of person-oriented modeling (POM). The components of the Framework are then presented in a systematic manner, technical issues are discussed, and a modular design for a computer program that could implement the Framework is presented.

The Framework is built on a three concepts. First, comprehensive chemical exposure models must begin and have a well-developed characterization of the person(s) exposed. Second, the models must separately simulate 1) multiple exposures to an individual at a specific time, 2) temporal (or longitudinal) changes in the individual and their exposures

as a series of discrete time steps, 3) variation across individuals, and 4) the uncertainty in these estimates. These four levels are captured in the programming by using four nested loops (Exposure Event Loop, Time Step Loop, the Inter-individual Variation Loop, and finally the Uncertainty Loop). Third, a taxonomy of temporal change is proposed that allows the integration of data from multiple sources into a simulation of an individual longitudinal exposure.

These concepts are not novel. They form the basis of many of the models reviewed in Chapter 2. However, these concepts have not been systematically described in the published literature. Nor has any exposure program fully implemented all of the concepts.

Together the three concepts result in an approach that is flexible, internally consistent, and allows the efficient use limited data sets. Using the Framework, a design for cumulative and aggregate exposure is developed that can be applied to any type of chemical exposure, including longitudinal exposures to multiple chemicals, by multiple routes, over any time period form a few minutes to a lifetime. The approach can track exposures and exposure related effects that cross generations. The approach can also be integrated with PBPK and PBPD models to predict the occurrence of adverse effects in the exposed population.

In Chapter 4, the Framework is applied to four exposure scenarios in an exercise developed by the Exposure Technical Implementation Panel of the American Chemistry Council's Long Range Research Initiative. Each of these four scenarios defined a population, a set of exposure sources, and a time period. In this exercise, the project team developed a systematic description of a software program that achieved the objectives of each of the scenarios using the Framework.

The results of the exercise are used to identify data gaps that could form the basis for future research. These data gaps are presented in Chapter 5 and include, additional data on the micro and macro behaviors that bring persons into contact with chemicals including data on contact duration and frequency for residential surfaces. Information on how these behaviors vary over persons (inter-individual variation) and how do they vary over time for a person (intra-individual variation). In addition there is a major need for data on HPV chemical in consumer products that would the concentration of the chemicals in the products; the frequency and manner that the products are used; and the demographic factors that could be used to predict the probability of use. Finally, improvements for indoor air models are recommended.

Chapter 1. Introduction

There has been a growing awareness in recent years that a person's exposure to a chemical or multiple chemicals may occur via multiple routes from multiple sources. To adequately evaluate such exposures, the scientific community requires models that can predict the occurrence of exposures for each potential combination of pathway and source, and then accumulate these exposures over time. Ideally, such models will account for variations in people's activity patterns that are influenced by age, gender, occupation, and other demographic factors. These activity patterns should account for the movements of individuals through microenvironment that are consistent with the season of the exposure, the geographical location and the demographics of the individual.

The Comprehensive Chemical Exposure Framework (Framework) is intended to show the structural relationship between the principal components of a model to estimate multi-route, multi-pathway[1], and multi-source for multiple chemicals over time. The development of this Framework is intended to achieve the following purposes.

1. Provide a systematic process for assessing comprehensive exposure to a chemical or chemicals.
2. Provide a basis for constructing computer software that will model comprehensive chemical exposures.
3. Demonstrate how exposures from such diverse sources as diet, water, the workplace, use of consumer products, indoor air, vehicles, refueling, and ambient air.
4. Use the Framework to identify data gaps in current knowledge of exposure modeling and exposure related factors.

Need for Tools to Characterize Comprehensive Chemical Exposures

There are a number of drivers for the determination of total exposure to a chemical or chemicals. Risks from a chemical occur as the result of the total[2] exposure to a chemical. As a result, source-based regulatory programs may not protect persons having multiple sources of exposure. Unless the total exposure from all sources is assessed, there will be questions concerning the safety of a chemical. The goal of assessing total exposure to a chemical has been around since the passage of TSCA in the late 1970s but has gained increased attention because of the passage of the Food Quality Protection Act of 1996and new programs focused on exposures of children. In addition, even programs that focus on a single source such as the Safe Drinking Water Act, Clean Water Act, and the Clean Air

[1] In this report, the term multi-route refers to the route of intake (oral, inhalation, or dermal intake). The term multi-pathway refers to the specific media through which a contaminate travels to reach the exposed person and the processes that determine that movement.

[2] The term total exposure will be used in this report to mean multi-route multi-source exposures and is equivalent to the term aggregate as defined by EPA for pesticide exposure. Total is also meant to include internal doses from the metabolism of other chemicals and endogenously produced chemicals such as acetone and formaldehyde.

Act require the consideration of "other sources" of exposure to regulated chemicals. Finally, EPA is becoming more aggressive on the assessment of risks associated with mixtures.

Organization of this Report

This report begins with a review of current modeling efforts (Chapter 2). The goals of the review are to identify modeling approaches that are relevant to the development of the Framework. Chapter 3 presents the Framework, a discussion of key technical points that must be addressed in using the Framework, and a modular architecture for a software prog5ram that would implement the Framework. Chapter 4 presents an application of the Framework to four exposure scenarios. Chapter 4 also discusses the uncertainty in the assessment of the scenarios. Chapter 5 discusses the data gaps identified in this process.

Chapter 2. A Review of Ongoing Relevant Exposure Modeling Efforts

The initial step in this study is to perform a survey of existing software and ongoing projects to develop models of aggregate or cumulative exposures or models of source-specific exposures (pesticides, consumer products, waste sites, diet, etc.). This chapter describes the approach used to identify current models and ongoing projects, the projects identified, and relevant information identified in each program and modeling project. As discussed below, the approach proposed for this task focuses on the integration of exposure at the receptor (or person). As a result, we have focused on models that describe the exposure to individuals in populations and not models that describe releases to the general environment or fate and transport models. The fate and transport models seek to relate releases of contaminants from either point sources or general releases and the resulting temporal and spatial distribution of the contaminants in air water and soil.

Data for person-oriented models (POMs) can be divided into three general categories; the characteristics of the exposed individual, the occurrence of exposure events in individuals' lives, and the magnitude of the exposures and resulting doses that occurs by various routes during each event.

The Characteristics of the Individual

As discussed in Chapter 3, placing the individual at the center of a modeling approach is the key to the development of a successful model of cumulative and aggregate exposure to the HPV chemicals. Therefore, each model and modeling project will be reviewed to determine how the model defines (or fails to define) the exposed population. The characteristics of the exposed individuals generally fall into two categories. The first category is the physiological characteristics that allow the determination of the dose from a given exposure. These factors include body weight and surface area. The second are those characteristics of the person's activities (activity patterns, diet, tapwater consumption, breathing rates) lifestyle (region of the county, setting, type of residence, presence of a yard and garden, income, occupation, age, etc.) that are important for defining the probability of encountering a chemical.

If a model is longitudinal, following an individual through multiple microenvironments, then the definition of the individual must take into account the potential for change over time. A person's diet and activities change from day to day. Body weight and surface area increase as children age. Individuals change residences and jobs during their lives.

The Occurrence of Exposure Events in Individuals' Lives

These data describe the usage of products by individuals or the interaction with contaminants in air, food, water, or residential surfaces. Specifically it is the basis for determining if an exposure event happens to a given individual on a given day, and if it occurs, what are the intensity and other characteristics of the exposure. Such data is typically dependent on the characteristics of the exposed individual. For example, the

potential for occupation exposures is largely limited to adults. Exposures from consumer use of pool chemicals require the individual to reside at a home with a pool. The probability of living at a home with a pool will in turn be a function of the type of residence (single family or multi family) region of the US and setting (urban or rural). This type of data may be in the form of survey data or databases of products or models of how individual's change jobs or use products.

Each of the models and modeling projects will be reviewed to determine how the probability of occurrence of exposure events is modeled.

The Magnitude of the Exposures and Resulting Doses that Occur by Various Routes

This type of data is provided by the traditional source-to-dose models. These models range from the simple algorithms in RAGS (EPA, 1989) or the Office of Pesticide Programs Residential SOPs (EPA, 1997a; 1999a; and 2001a) to complex models using computational fluid dynamics (CFD). These models require tracking the amount of one or more compounds of interest in various compartments (paint on walls, detergent residues on surfaces of counters, chemicals in indoor air). The levels of residues in these compartments must also be modeled over time.

The models and modeling projects will be reviewed to determine the data and algorithms used in determining dose. This is likely to be the area where most information will be collected.

Identification of Existing Models and Ongoing Modeling Projects

Models are identified using a number of approaches. First, team members have been involved in probabilistic modeling of multi-route and multi-source exposures for more than 10 years and have extensive contacts with a number of the ongoing projects. These contacts were used to collect data on ongoing projects. Second, a review was performed of published summaries of models (Price and Heidorn, 1999; Pandian, 2001; Guo; 2002). Third, a review was performed on recent presentations at ISEA and SRA professional meetings. Finally a literature search was performed.

Literature Search

A literature search was performed using the search tools MEDLINE and SCIRUS. The search was performed using the following search terms:

a. Exposure models
b. Computer models of exposure
c. Aggregate Exposure
d. Cumulative Exposure
e. Multi-route exposure
f. Multi-source exposure
g. Probabilistic models
h. Stochastic models
i. Microenvironmental models

In addition, the search terms were also entered into the web search engine, Google. The search engine allows the identification of relevant government publications and other documents available on the Internet.

As a result, of this search 32 articles were identified on modeling projects relevant to this study. In addition, the web search identified a number of EPA reports and abstracts from professional meetings. The publications included references to the following models:

- PNEM
- CALENDEX™
- LifeLine™
- SHEDS
- CalTOX

Models and Model Projects Identified

Table 1 lists the models and modeling projects that were identified as potentially relevant to the construction of the Framework. In number of instances, older models are no longer supported or have been superceded by programs that are more recent. In these cases, the affected models were not considered further or the "family of models" were reviewed. Table 1 indicates which of the models were eliminated and which were considered in this report.

TABLE 1. MODELS AND MODELING PROJECTS IDENTIFIED
(Models in *Italics* were not Reviewed)

Aggregate and Cumulative Models Developed to Meet the Requirements of FQPA

Calendex™	CARES™
LifeLine™	SHEDS

"Tool Box" Models

MENTOR	THERdbASE
notita™	*EML/IMES*
PC-GEMS/RISKPRO	

Dietary Models

DEEM™	TAS DIET
DEPM	*PATHWAY*
CALDOS	

Review of Industrial or Waste Disposal Site Models

MEPAS	CALTOX
API DSS	MMSOILS
SmartRISK™	

Consumer Product Models

E-FAST	CONSEXPO-3
PROMISE	*WPEM*
DERM	*DERMAL*
USES	

Air Models

IXAQ	CPIEM
CONTAM	TEM
MCCEM	RISK
TRIM	

Indirect Models

AirPEX	BEAM
HEM	pHAP
pNEM	SHAPE
HAPEM	SCREAM

Occupational Models

Tool Box
ChemSTEER
EASE

These classes can be divided into the following general groups:

- Total source models
  - Models created to address the needs of FQPA
  - Other aggregate models
- Multi-route models of exposure
  - Local industrial or waste sites;
  - Tapwater;
- Models of exposures to specific sources or routes
  - Diet
  - Consumer products
- Model "tool kits";
- Indoor Air models; and
- Occupational Models.

Review of Aggregate and Cumulative Models Developed to Meet the Requirements of FQPA

This section presents a review of the models of multi-pathway, multi-source (aggregate) and multi-chemical (cumulative) exposure models that have been developed to meet the requirements of the U.S. Food Quality Protection Act of 1996 (FQPA). EPA's approach for implementation of that law and the technical issues raised by that approach are presented in its guidance on aggregate and cumulative exposures (EPA, 1999b, 2000a). FQPA amends the approaches for pesticide regulation under the Federal Insecticide Fungicide, and Rodenticide Act (FIFRA) and the Food and Drug Act by changing key concepts of risk on which regulatory decisions are based. FQPA requires that for non-occupational risk, all sources of exposure from a chemical and all chemicals with the same mechanism of toxicity are considered together in assessing risk. Further, special attention is focused on subpopulations and special periods of life. Children and women of childbearing age are a particular concern. Endocrine disruptors are of particular concern. Estimation of risk from such effects requires consideration of exposure over long periods of time. Under previous law, EPA had estimated risk to the population (defined in various ways) to individual sources of exposure such as food, tap water or residential products. As a beginning to implement FQPA, EPA must consider these sources together in an exposure and risk assessment[3]. Traditionally, ambient airborne sources of exposure have not been a subject of regulatory concern, in part because of the low volatility of pesticides other than fumigants. To date, EPA has not considered this source to be a high priority for the aggregate/cumulative assessment paradigm.

CALENDEX™ and CALENDEX-FCID™

Calendex™ and Calendex-FCID™ are trade secret[4] software programs developed by Durango Software and licensed through Exponent, Inc. The information supporting this

[3] Occupational risk remains separate; however, because it is not the subject of the FQPA legislation.
[4] Trade secret software is software where the code is not released by the owner and is held as a "trade secret". Users have access to use the program but not to examine or verify the model's operations.

summary was presented at the FIFRA Scientific Advisory Panel (SAP) on September 27, 2000[5]. In the documentation for the review of the software by the SAP, Exponent, Inc. and Durango provide their perspective on the objectives for its design and development. Calendex™ is described as a "Calendar-Based Dietary and Non-dietary Aggregate and Cumulative Exposure Software System". The objectives of the developers, as delineated by them, include:

- To provide estimates of exposure that are statistically representative of the U.S. population as well as a wide range of user-specified subpopulations;
- To estimate exposure to single or multiple compounds for a variety of time periods from residues in food, in or around the residence and from occupational uses of the chemical;
- To aggregate exposures "as appropriate for the scenarios under consideration;"
- To assess the cumulative exposure from multiple compounds that have a similar mode of action toxicologically;
- To incorporate temporal aspects of exposure, as with changing chemical concentrations of a chemical over time;
- To account for spatial aspects of exposure; and
- To yield simple point estimate exposure analyses or probabilistic estimates based on distributions and Monte Carlo analysis techniques.

Many of these objectives are common to other models responding to the challenges presented by FQPA, although the approaches employed in this model may be quite different from those in other models (ILSI, 1997).

Platform/Model Design

The Calendex™ architecture is a two-part structure, the first being the dietary analysis module, DEEM™ and the second part constructed to calculate the non-dietary component of the aggregate and risk. Cumulative assessment is accomplished by using the relative toxicity approach for multiple chemicals. The toxicology metrics that define the common mechanism endpoint for all of the chemicals is used together with a relative potency factor for each chemical. The individual exposure assessments for a chemical is corrected using this factor and the exposure assessments can then be compiled across all chemicals.

In the non-dietary component of the model, the user supplies three types of data.

1. Use pattern information of products of interest with the frequency of application and amount of product applied;
2. Environmental concentration data on days before, during and after treatment (residue factors); and

[5] Calendex™: Calendar-Based Dietary and Non-Dietary Aggregate and Cumulative Exposure Software System, Petersen et al. Novigen Sciences and Petersen, Durango Software. Documentation presented to FIFRA SAP, September 27, 2000. Source: www.epa.gov/scipoly/sap/2000/september/calendex. The developers participated in the International Life Sciences Institute (ILSI) workshops dedicated to the design of models for aggregate exposure assessment where many of the features of the models were discussed in detail (ILSI, 1997,1999). These concepts have also been presented, in whole or in part, at scientific meetings including the International Society for Exposure Assessment in October 2000.

3. Exposure factors such as body weight, breathing rate, and activity patterns (contact factors). These factors are supplied by the model and in some cases may be modified by the user.

Calendex™ contains information utilized in the exposure analysis. The information is arranged in a series of "libraries" that are available to the user to structure the analysis.

What is the Population Modeled?
The objective of the software is to provide exposure and risk assessments that are representative of the contemporary U.S. population and subgroups of that population. The model utilizes the USDA Continuing Surveys of Food Intakes by Individuals conducted by USDA. At the time of the September 2000 SAP review and documentation provided for that review, Calendex™ utilized data from the 1989-91 and 1994-96 surveys. Since that time, the 1998 USDA Supplemental Children's Survey was added to the database in the software. These data provide two important types of information. The first is a detailed diary of a person's diet during each of the two or three days of the survey. These data are used in the dietary assessment, described in the review of DEEM™. The second set of information is the demographic data collected as part of the survey. Each respondent was asked to provide data about their weight, height and information about their household income, education and factors that could influence dietary profiles. For children, the primary adult provided such information. Calendex™ stores selected demographic data in the CSFII Library. The data include respondents' ages, body weights and heights. The dietary intake information is used in the DEEM™ model.

The surveys were conducted over three days for each respondent in the 1989-91 survey and over two non-contiguous days in the 1994-96 survey. Not all respondents completed all days of the survey. In addition, the survey was intentionally designed to focus attention on the lower socio-economic populations. The 1998 USDA Supplemental Children's Survey was designed to provide a robust dataset on children that could be combined with the 1994-96 survey. USDA provided statistical weights that adjusted for the different probabilities of selection and non-response rates and permitted data from the 1998 survey to be added to the 1994-96 data. These weights were derived for persons completing the first day of each survey and for persons who completed all days of the survey. The weights are designed to correct the results for the individuals in the survey so that the distribution of the weighted sample becomes more aligned to the actual U.S. population demographic characteristics. Fourteen demographic characteristics were used for this weighting exercise. To define the population, Calendex™ uses records and sample weights for those respondents who completed all days of the respective surveys. Records of individuals who may have completed only one or two days are apparently eliminated, although the CSFII library in Calendex™ does not permit the user to modify or eliminate any records included in the library.

The user of the software may create population subgroups based on gender, age, season, or region. Data in the CSFII library are binned accordingly for the analysis. If a non-dietary and dietary scenario are to be considered simultaneously, the user defines the

demographics of interest at the initiation of the analysis and the DEEM™ module creates the dietary profile using both the demographic and food consumption components of the CSFII data. The demographic components from the dietary analysis are then linked to the non-dietary analysis by using matching demographic data (weight, height, etc) data from the model's CSFII library as necessary for the non-dietary component. In this way, the demographic profiles of a person considered in the dietary analysis are roughly equivalent to the demographic profiles for the non-dietary analysis to which it is pared.

Methodology for Modeling Interindividual Variation in the Population
The developers describe the objective of the non-dietary exposure assessments as characterization of the exposure to the population or subpopulation of concern, and to identify the variability associated with that exposure. Interindividual variability can be introduced via many parameters used in the calculation of exposure, including variations in opportunity for exposure, variations in the quantity of the compound available in any exposure opportunity, variations in physiological characteristics defining exposure elements, variations in spatial or temporal aspects of the exposure as well as other factors. Some of these elements are involved with intra-individual variability also. A given person will have variability in their exposure opportunity, the amount of compound available to them on any exposure event, and the physiological changes in the person over time, even if presented with the same opportunity and same amount of compound during that event.

Calendex™ uses either point estimates for the various parameters or distributions of the residues and other parameters in a Monte Carlo probability analysis. These distributions may reflect both uncertainty and variation. In both cases, residues in the medium are multiplied by the contact amount to determine the exposure estimate for this exposure route. In the dietary component, DEEM™, the analogous calculation is made: the residues in food are multiplied by the amount of the food consumed. This can be done for many people, using point estimates or using distributions of residues with distributions of contact amounts (or food consumed). Each exposure iteration can be repeated up to 5000 times for each participant in the CSFII survey records.

Interindividual variation can be characterized in at least two ways with this approach. First, groups of individuals are defined by the binning of records according to age categories. The output of the analyses presents exposure metrics for the different sub-populations as defined by that binning. In addition, within a sub-population, variability is reflected in the distribution of products yielded by the above calculation.

However, the variability represented among individuals in the resulting distribution of exposures may also represent intra-individual variability. Each exposure iteration may be repeated up to 5000 times for the same record of an individual in the survey. The final exposure distribution thus reflects both intraindividual variability (multiple exposures for the same individual) and interindividual variability (exposures calculated for different people within the same subpopulation).

Durations of Time Addressed by the Model
Four time periods of exposure duration are considered in Calendex™: daily/acute, short-term, intermediate-term, and chronic (up to one year). Longer durations of exposure are computed by adding the daily exposures across the selected period of exposure and dividing by the number of days considered. This presents a time-weighted average across the chosen duration. The user may specify the type of duration to be considered, guided by the toxicology information that suggests the duration of dosing that is required to elicit a specified biological effect.

Sources of Exposure Evaluated
Diet
Exponent's Dietary Exposure and Evaluation Model (DEEM™), also developed by Durango Software and licensed through Exponent, provides the entire dietary exposure analysis capabilities of Calendex™. The features of that model are considered in this review under discussion of dietary models.

Tap water
Exposure from drinking water is calculated as the product of consumption rat and a residue concentration. The consumption estimates are derived either from CSFII data or data in EPA's Exposure Factors handbook. Apparently, the user supplies these data and then they are combined in the equation with user-supplied information about residues of the pesticide in the drinking water. Those data may be supplied by registrant studies or publicly available government surveys.

Residential Sources of Exposure
Non-dietary exposure scenarios presented in September 2000 included turf applications, pet pest control products and indoor applications. Dermal and oral routes of exposure are considered for these scenarios. The calendar approach allows the user to prescribe the dates of pesticide use according to information about the product use, market data or other climate, regional or seasonal use that is known by the user. The model can adjust the level of the chemical residue for days subsequent to the day of use by applying degradation functions. It also considers elapsed days between applications days and the day of use of each chemical. Residential sources that may be considered within Calendex are defined by the equations contained in the Equation Library of the model. Additional equations are added by the developers over time, but a listing of those options was not available for this review.

Approach for Addressing Uncertainty
The software developers have described how Calendex™ addresses the three categories of uncertainty: scenario uncertainty, parameter uncertainty and model uncertainty.

Scenario uncertainty includes descriptive errors, aggregation errors and incomplete analysis. There are several possibilities for error when the user has limited information about the use of chemicals in the home, on crops, across seasonal and geographical regions. Additional error can be introduced by the unknowns about human activity within the home environment, such as time spent in various rooms or activities in those

rooms. Since the user sets up the pathways of concern and applies the data relevant to those pathways, the user-supplied uncertainty may result from errors in judgment by the user. Limitations of knowledge about the general use of the chemical and details on the chemical-specific parameters are key to the magnitude of the uncertainty here.

Calendex™ addresses scenario uncertainty by suggesting that separate analyses may be conducted using different assumptions and considering the differences in the resulting analyses.

Parameter Uncertainty includes measurement errors, sampling errors, variability and use of surrogate data. As with any model that uses data and assumptions, the intrinsic errors, bias and uncertainties of any parameter will be assumed by the composite of those parameters. Calendex™ developers noted some of the obvious errors, bias and/or uncertainties contained in data sets used by the model. CSFII respondents may have provided incorrect information about their weights, heights and amount and types of food eaten. Those errors may be overestimations or underestimations. For any one respondent, there may be both types of error in their reports. The Calendex™ developers correctly point out that the result of such errors may be an under-calculation of exposure and risk, or an over-calculation. No solution is provided for identifying such uncertainty when it occurs, or how to assess the magnitude of such.

Model uncertainty is introduced by the inappropriate application of information into the model or incorrect choice by the user for the parameters, algorithms or other particulars in setting up the analyses. Since the user defines the equations to be employed, professional judgment on the part of the user becomes a very prominent factor in the overall uncertainty presented by the model.

Calendex™ does not have a built-in uncertainty analysis tool and the developer recommends, "conducting multiple sets of exposure analyses to capture the impact of the critical factors that are identified in the steps leading up to the analyses."

Cumulative and Aggregate Risk Evaluation System (CARES™) Version 2.0
History and Purpose of the Model

CARES™ is owned by Crop Life America (CLA) with input from a variety of stakeholders. The purpose of the software is to determine aggregate risks from drinking water, residential and dietary exposure for a single pesticide and cumulative risks from pesticides that have a similar mechanism of toxicity. Version 2.0 of CARES was scheduled for release in June 2003.

The following summary is based upon information obtained from the project's web page and data and information released with Version 1.0. This information has been supplemented by information obtained from personal communications with CARES™ team members[6].

[6] Personal communications with Muhilan Pandian on the topics of model design, platform, and relationship between CARES and notita™.

Platform/Model Design

CARES is largely written in Visual Basic with parts written in C++. CARES will run in the Windows® environment. While CARES is available as a stand-alone program, Notitia™, a trade secret software program owned by infoscientific.com, Inc., serves as the software engine that runs CARES and houses data used in CARES.

CARES consists of a series of modules:

1. Population Generator
2. Residential Model
3. Dietary Model
4. Water Model
5. Aggregation and Cumulative Calculators
6. Contribution and Sensitivity
7. Risk Assessment
8. Graphics and Reporting

What is the Population Modeled?

Because CARES is intended to support regulatory decisionmaking, the model's focus is the general U.S. population. However, the output of the model will allow the user to separately evaluate risks by subpopulations defined by age/gender, Race/ethnicity, and geographical region. These subpopulations include:

Age/gender
Race/ethnicity
Regions and Sub-regions

Due to the approach used, the user may not be able to investigate risks by more than one of the categories. Thus, analyses by region and age group, or age group and Race/ethnicity may not be permitted.

Methodology for Modeling Interindividual Variation in the Population

The CARES project has developed a novel approach for characterizing interindividual variation. This approach creates a "Reference Population". This population is defined by sampling the Public Use Microdata Sample (PUMS) of the 1990 U.S. census (Census, 1992). The Reference Population consists of 100,000 individuals. The individual have been selected to match the US population (as measured by the 1990 Census). The number of 100,000 was selected as being sufficiently large to allow a minimum of 5,000 individuals in each of the above subpopulations. (However, combinations of classes Race/ethnicity and Age/gender may or may not meet the criteria of 5,000 individuals).

Data extracted from the census include:

1. The number of people in the U.S. population represented by the individual (i.e., the sampling weight)
2. Age

3. Gender
4. Race (including Hispanic origin codes)
5. Location: region, division of the region, state, and PUMA
6. Location: metropolitan area or other
7. Number of persons in the individual's household
8. Household income indexed to a reference year
9. Household income as a percent of poverty level
10. Household percent poverty category
11. Employment status
12. Educational attainment
13. Occupation categories
14. Ownership status of individual's housing unit
15. Household structure characteristics
16. Type of household
17. Source of water

These data are used to establish what is called a vector of individual characteristics (VIC). The VIC consists of values that never change, the VIC Kernel, and portions that change VIC Augmentation. The VIC Kernel is composed of data from the census called "real data" and data from other surveys, which is called "attributed data".

The CARES project then uses the "real data" in the VIC to select "attributed data" on the individual's physiology and food consumption. Physiology data is selected from one of the 21,269 individuals in the 94-98 Continuing Survey of Food Intake by Individuals (CSFII). This selection of data was performed by matching a person's record in the Census data with a person's record in the CSFII.

Special notice should be given to the approach for matching individuals developed in CARES. First, CARES established a series of absolute rules:

- Data on males will be only matched with males and female data with females;
- For children (ages less then 20) all age matching will be on an age basis.

Second, within these age and gender categories, individuals are matched based on a pattern recognition technique. This approach assigns each individual in the 100,000 Reference Population and each individual in the 94-98 CSFII survey a location in a seven-dimensional space that is defined by the following parameters:

- Region of the US (four census regions);
- Setting (urban or rural);
- Household size;
- Race and ethnicity;
- Household income;
- Income as a percent of poverty
- Poverty category

In setting up this space, the parameters are weighted based on how important the parameter was in terms of predicting types of food consumed by the individual.

Differences in parameters that greatly affected food consumption were given greater consideration than parameters that did not affect food consumption.

The individual from the CSFII that is nearest to each individual in the reference population is matched to that reference population individual. Once the individual is matched, three pieces of information are moved from the CSFII to the VIC:

- Self-reported body weight;
- Self-reported height;
- Pregnancy status;
- Dates when food consumption survey(s) were completed;
- For children aged <1, Age in Months;
- One or two days of food and tapwater consumption.

As discussed below, CARES models exposures that occur over a period of year. The body weight and height were kept constant over this period for adults who were not pregnant. Individuals with ages less than 20 had their heights and weights adjusted to reflect the potential for growth. Pregnant women have their weight adjusted over time to reflect gestational changes in weight. These data make up the fixed portion of the VIC, called the "VIC Kernel". These data are fixed by the CARES team and cannot be changed by the user.

Using the VIC Kernel, the CARES model selects data on daily consumption of food using the same pattern recognition approach. The VIC Kernel specifies food consumption for either one or two days of the modeled year[7] the remaining days are selected using a variation of the pattern recognition approach.

In this approach, each individual in the reference population has a unique CSFII record. This record is again placed in an n-dimensional parameter space along with the other records of the dietary portions of the CSFII survey that occur on the first of the remaining days of the modeled year. The model then identifies the 3-5 nearest neighbors and randomly selects one of the 3-5 nearest neighbors. That record is then assigned to that day. This process is repeated for the other days of the modeled year. Each time the model only considered the CSFII dietary records collected for that day of the year.

Because of the short period of duration, the model does not allow the modeled individuals to live in more than one house. Thus, residential mobility is not considered.

Durations of Time Addressed by the Model

CARES limits its simulation of individuals' lives to a period of one year. The year is defined as beginning with each simulated individual's birthday and proceeding for 365 days. Each day is tracked in terms of the day of the week and the season of the year. The

[7] Since birthdays can happen on any day of the year. The modeled year actually take up three calendar years. However, since CARES is not a model of any specific year or set of years this distinction has little meaning.

dates of birthdays are randomly assigned different calendar dates based on data taken from the CSFII.

The basic unit of exposure in CARES version 1.0 is a single day. Each day's exposure is determined by summing the doses that occur from a series of events that occur during the day. These events include meals, tapwater consumption, and residential exposure to the residues from specific microenvironments. These events may be of a few hours or minutes duration. While each event's route-specific exposures and doses are determined individually by the model, the exposures are summed to produce estimates of daily exposures the end of the simulation of each day. Thus, the shortest period evaluated in the model's output is a single day. The software allows the user to track the average dose that occurs over any number of days from 1 to 365 days.

Sources of Exposure Evaluated

CARES is constructed to support EPA and the regulated community in meeting the requirements of the FQPA. The FQPA specifies that EPA will determine the aggregate and cumulative risks associated with pesticides used on agricultural products and in residential environments. The exposures to pesticides used on agricultural products will also consider tapwater exposures. As a result, the model focuses on exposures to pesticide residues in food, tapwater, and in residential environments.

Diet

CARES dietary module accepts data on contaminants that occur in agricultural commodities this approach is shared by the DEEMs/CALENDEX and LifeLine™ Model. The contaminants can be described in terms of a single value or as a parametric or non-parametric distribution. These materials may be naturally occurring substances (metals taken up from soil or organic compounds that naturally occur as a component of the commodity) or materials added to the crops (pesticide residues or food additives). The software is capable of addressing the impact of food processing, handling, and storage on the residues.

The process begins by pulling a dietary record from USDA's Continuing Survey of Food Intakes by Individuals (CSFII). This record specifies the specific food items and amounts of the items consumed by the individual. The distribution of residues in each of the food items is modeled based on the distribution of contaminant levels in the commodities used in the recipe for a food item and the amount of the item an individual consumes. The total oral dose for a given day is determined by summing the dose from each food item consumed on a day. CARES intends to use the 1994-1996, 1998 CSFII, with the FCID recipe files (referred to the as translation files) developed by USDA.

As discussed above the proposed design for the program calls for assigning dietary records taken from multiple individuals to each day of a single individual's simulated life. The doses from these records are used to create an exposure history for the individual.

Tapwater
As discussed above, CARES determines exposure to contaminants in water supplies that occurs by direct ingestion. The model does not consider exposures from non-ingestion pathways (dermal contact and inhalation during showering).

Residential Sources of Exposure
Figure 2 presents the draft design of the residential module of CARES. The approach for residential exposures is built around the exposure scenarios and the resulting exposure/dose equations given in EPA's Residential SOPs (EPA 1997a, 1999a, 2000b, and 2001a). The scenarios are limited to those relevant to pesticide use and include:

- Residential Lawns
- Crack and Crevice and Broadcast Treatment
- Garden Plants
- Trees
- Swimming Pools
- Painting and Wood Preservative Treatments
- Fogging
- Pet Treatment
- Detergent / Hand Soap
- Impregnated Materials
- Termiticides
- Rodenticides
- "Pick Your Own"

Details provided by the user on each product are used to estimate residue levels for:
- Pesticides on the surfaces of indoor microenvironments,
- Pesticide levels in air,
- Pesticide levels on turf and in soil (for pesticides used out of doors).

The user is also required to enter data on the frequency of use of the pesticide and how the use will vary by time of the year, day of the week, and the fraction of homes that will use the product. This data is used in a port of the program called an event generator. The event generator uses an annual frequency of use and the correlations with seasons and days of the week to generate a synthetic history of usage of the product. CARES will also allow the use of the results of the IRJV survey when it becomes available.

Approach for Addressing Uncertainty
CARES focuses entirely on variability. The model is amenable to performing sensitivity analyses.

LifeLine™ Version 2.0

THE LIFELINE GROUP

The LifeLine™ Model Version 2.0 (LifeLine™) was created by The LifeLine Group[8] (LLG) a nonprofit organization created "to advance scientific knowledge in the field of toxic chemicals". LifeLine™ is an ongoing project with additional versions under development. LifeLine™ Version 2.0 can be obtained without charge at http://www.thelifelinegroup.org. The code for the software is copyrighted but is not held as a trade secret. Copies of the code are available upon written request for the purpose of verifying how the program operates.

LifeLine™ was created as a tool for the assessment of aggregate and cumulative exposures to pesticides in support of the regulatory decisionmaking under the Food Quality Protection Act. The model addresses exposures that occur from the use of pesticides on agricultural crops, in residences (homes and yards), and pesticide residues that occur in water supplies. The model determines the aggregate and cumulative doses that occur from these exposures and the risks associated with such doses.

The model can be used to characterize exposures to the active and inert ingredients of pesticides used on a variety of agricultural commodities. The model can also be used to evaluate any substance in the food or tapwater where the levels of contamination can be specified in different agricultural commodities or tapwater supplies.

Platform/Model Design

LifeLine is written in C++ and is a stand-alone program that runs on Windows® 95 Windows® 98 and Windows® NT and later versions of Windows. Outputs from the model can be evaluated using database programs such as dbase®, Access™, and Excel™. The program consists of six separate models/modules:

1. Residue Translator – Allows the user to enter data on residues in agricultural commodities on an annual and seasonal basis.
2. Active Ingredient and Product Description – Allows the user to enter data on the physical chemical properties, toxicity, and residential usage
3. Tapwater Concentration – Allows the user to enter data on the distribution of contaminants in various water supplies, by region, and season.
4. Activity Description - Allows the user to enter data on key exposure factors used in the residential exposure assessment.
5. The LifeLine Model – Performs the simulation of aggregate and cumulative exposures and doses using data entered directly by the user or through one of the four modules listed above.
6. The Risk-Dose-Exposure Model – Facilitates the analysis of the outputs of The LifeLine model allowing the user to:
   - Determine the factors that drive high levels of exposure, dose and risk;
   - Analyze doses and risks by age and season, and;
   - Create and export data files.

[8] LLG is the primary contractor for this report.

What is the Population Modeled?

Because the model was intended to support regulatory decisionmaking, the model's focus is the general U.S. population and subgroups defined by gender, race, income, ethnicity, region of the U.S., season of the year, and the age of the individual.

Methodology for Modeling Interindividual Variation in the Population

LifeLine™ seeks to model the interindividual variability and the longitudinal intra individual variability of the individuals that make up the US population. LifeLine™ models longitudinal variation of individuals over their lifetimes starting with the characteristics of the individuals at birth. LifeLine™ begins the modeling of individuals' birth characteristics based on data taken from the National Center for Health Statistics (NCHS) Public-use - database of birth records for 1996. These records are used to determine the permanent characteristics of the individual.

The assignment of the individual to a socioeconomic quartile is based on the information in the mother's education contained in the natality database.

Once the characteristics of the individual are established, this data is used to guide the simulation of the physiological characteristics of the person throughout his or her life and the number and individual characteristics of the homes she or he will reside in during the simulated life.

Physiological characteristics are based on longitudinal models of growth that have been developed using nationally representative data collected in the Third National Health and Nutrition Examination Survey (NHANES III).

Residential characteristics of the individuals' homes are modeled in two steps. First, the residential mobility of the individuals is modeled to determine the type, setting, and region of each home the individual will reside during his or her lifetime. This modeling is performed using data from the Current Population Statistics, US Census. Based on the type of home and the individual's SES, a record from the American Housing Survey is selected and used to describe the characteristics of the home (type and number of rooms, lot size, finished floor space). These data are used with a data set on relative room sizes developed by the LifeLine Group and published values for whole house exchange rates.

Finally, the data on the age, season, and gender are used to select the data on dietary consumption and data on age, gender, region, season, and day of the week (a weekend day or weekday) are used to select a record from the National Human Activity Pattern Survey (NHAPS).

Durations of Time Addressed by the Model

The model simulated the individuals' lives from birth to 85 years. Because of the lack of robust data for individuals older than 85 years, LifeLine™ Version 2.0 does not attempt to model exposures to individuals with ages greater than 85 years.

The user has the option of either specifying a fixed lifespan for all individuals in the simulated population, or using standard mortality statistics to predict an age of death for each individual. In the first case, LifeLine™ simply models the selected number of years of life for every individual. In the second case, mortality is modeled probabilistically for every individual on an annual basis (i.e., an individual's life is defined in terms of a whole number of years). The basis for modeling mortality is the Life Tables published by NCHS as part of the 1995 Vital Statistics of the U.S.

The simulation of exposure is closely linked to seasonal but not secular trends. The model assigns a birthday (a specific day of the year) based on the natality record drawn for the individual. Based on this assignment, the model tracks the season and the individual's age for each day of the person's life. Thus, each simulated person is consistently defined in terms of their age and the season for their exposures. This definition allows the consistent determination of age- and season- related changes in exposure inputs. However, Version 2.0 of LifeLine does not include a provision to model exposure sources that change from year to year. As a result, the concentrations of pesticides for each season are assumed to be constant over multiple years. Thus, secular trends in exposure are not addressed in Version 2.0.

The basic unit of exposure in LifeLine™ is a single day. Each day's exposure is determined by summing the doses that occur from a series of events that occur during the day. These events include meals, tapwater consumption, and activities occurring in specific microenvironments. These events may be of a few hours or minutes duration.

While each event's route specific exposures are determined individually by the model, the exposures are summed to produce estimates of daily exposures at the end of the simulation of each day. Thus, the shortest period evaluated in the model's output is a single day.

The software allows the user to track the average dose that occurs over any number of days from 1 to 365 days. In addition, seasonal, and annual doses are tracked for each year of an individual's life. Finally, lifetime average doses can be determined for each individual.

Sources of Exposure Evaluated

LifeLine Version 2.0 assesses exposures to pesticide residues in food, tapwater, and in residential environments. While pesticides are the focus of LifeLine™, the model can be applied to a material where the distribution of residues can be specified to occur in specific agricultural products (specific fruits, meets, grains, etc.) or to any material where the distribution of residues in tapwater can be specified.

Diet

LifeLine™ Version 2.0 contains a model of exposure to contaminants that occur in agricultural commodities. The contaminants can be described in terms of a single value or a distribution. The residues can be related to the season in which the commodity is consumed. These materials may be naturally occurring substances (metals taken up from soil or organic compounds that naturally occur as a component of the commodity) or materials added to the crops (pesticide residues or food additives). The software is capable of addressing the impact of food processing, handling, and storage on the residues.

The process begins by pulling a dietary record from USDA's Continuing Survey of Food Intakes by Individuals (CSFII). This record specifies the specific food items and amounts of the items consumed by the individual. The distribution of residues in each of the food items is modeled based on the distribution of contaminant levels in the commodities used in the recipe for food item and the amount of the individual commodities. The total oral dose for a given day is determined by summing the dose from each food item consumed on a day.

LifeLine™ Version 2.0 allows the user to calculate dietary exposures using either of two versions of the CSFII. The user may select the 1989-1991 CSFII, with associated food recipe files. Version 2.0 also, however, allows the user to select the 1994-1996, 1998 CSFII, with associated recipe files (referred to as translation files) developed by EPA and USDA. Additional information on diet is given in Chapter V.

Tapwater

Version 2.0 of LifeLine determines exposure to contaminants in water supplies that occurs by direct ingestion, dermal contact during showering, and inhalation during showering. The user is allowed to specify the range of contamination as a function of season, region, source of water, and setting (urban/suburban versus rural). Tapwater consumption can be based on data from the CSFII surveys or from age specific defaults. Estimates of dermal and inhalation exposure are based on EPA models of diffusion from dilute solutions, and showering models.

Residential Sources of Exposure

Version 2.0 of LifeLine assesses exposures to pesticides that occur from the treatment of residential pest by the homeowner or by professional pest controllers. The model begins by focusing on pest pressures (the probability that a specific pest will require control on a residence). Based on a residence's pest pressures, the model simulates the probability that a specific pesticide product is used on a given day in one or more microenvironments. Details provided by the user on each product are used to estimate residue levels for:

- Pesticides on the surfaces of indoor microenvironments,
- Pesticide levels in air,
- Pesticide levels on turf and in soil (for pesticides used out of doors).

Once the process is completed, data on individuals' activities are used to define the interaction of the individual with the residues in a specific microenvironment. These interactions include:

- Inhalation of air containing pesticide residues,
- Dermal contact with hard surfaces (hard floors),
- Dermal contact with soft surfaces (carpet),
- Dermal contact with turf,
- Oral exposures from mouthing events, and
- Incidental consumption of soil and grass.

Based on this interaction the exposures and doses that occur because of the interaction are determined. The process can be summarized as follows.

Pest Pressure → Product usage → Residue levels → Exposures → Doses

The residence is defined as a set of up to 12 indoor and 2 outdoor microenvironments were pesticides are used.

By dividing the home into microenvironments, activities (as defined by databases of activity patterns such as NHAPS activity data or CHADS) that are unique to a specific room (kitchen or bed room) can be linked to data on the patterns of pesticide usage.

Stochastic Human Exposure and Dose Simulation (SHEDS)

SHEDS is a family of models that include research programs and program that have been released for general use. SHEDS is part of NERL's research program to develop probabilistic human exposure source-to-dose human exposure (HES2D) models that estimate multimedia and multipathway pollutant exposures of general as well as at-risk populations. The HES2D is being designed to predict and diagnose complex relationships between pollutant sources and dose received by different population sub-groups, e.g. children and the elderly. HES2D incorporates models, databases, and analytical tools within an integrated modeling framework. The methods and models developed under this research program will provide estimates of variability and uncertainty in the predicted exposure distributions and characterize factors influencing high-end exposures. These models will address both aggregate (all sources, routes, and pathways for single chemical) and cumulative (aggregate for multiple chemicals) exposures.

First-generation versions of SHEDS models have been developed for particulate matter (PM) and pesticides. The particulate matter version SHEDS-PM is designed to work in conjunction with MENTOR, see Chapter IV. SHEDS-PM is collaboration between NERL scientists and external scientists from Environmental and Occupational Health Sciences Institute (EOHSI) and Lawrence Berkeley National Laboratory (LBNL) under competitive agreements (cooperative agreement with EOHSI and IAG with LBNL).

The SHEDS model for pesticides (SHEDS-Pesticides) is being developed in stages. The first generation SHEDS-Pesticides focused on children's exposure and absorption on a single day post-pesticide application via dermal contact with and non-dietary ingestion of surface residues in and around the home. It also allows for characterization of uncertainty as well as variability in predicted population estimates of exposure and dose. The algorithms for dermal exposure and the temporal framework for SHEDS-Pesticides were initially developed as the doctoral thesis of Dr. Valerie Zartarian and is part of the Stanford University model DERM (Zartarian, et al. 2000).

The second-generation SHEDS-Pesticides extends the first generation model by including the inhalation and dietary ingestion routes in addition to dermal contact and non-dietary ingestion. The algorithms used to estimate exposure via the various routes and pathways will been refined. The refined model is intended to simulate an individual's exposure for periods up to several years. In addition, a user-friendly interface is being developed for the SHEDS-Pesticides model with both exposure researchers and regulators in mind as potential users.

A version of SHEDS for exposure from contact with pesticides applied to wood, SHEDS-Wood has been released (EPA, 2002) and can be downloaded at http://www.epa.gov/scipoly/sap/2002/index.htm.

Platform/Model Design

The initial and second generations of SHEDS-Pesticide are constructed in SAS and are intended to run on the PC. Use of SHEDs requires the use of SAS version 8.1. Future versions may be built on multiple platforms.

What is the Population Modeled?

SHEDS-Pesticides is based on the CHADS database (see http://www.epa.gov/chadnet1/). CHADS is a compilation of data on activity patterns from multiple surveys. Individual's characteristics and geographical and seasonal assumptions are assigned based on data in individual CHADS records. In this way CHADS serves the same function as the CSFII records in Calendex™ and CARES™.

SHEDS-PM is integrated with MENTOR. MENTOR is a geographically based model that included data on the location of individuals through out the U.S. by census tract. Thus, the model can focus on any subpopulation defined down to census tract. Based on the demographic data for the census tract the model can identify the number of residents in each census tract that fall into various age and gender categories.

Methodology for Modeling Interindividual Variation in the Population

The two SHEDS models use two different approaches for defining the interindividual variation in exposure and dose. The initial version of NHAPS-pesticides is dependent on

the population defined by NHAPS. The model simply selects records from the data set and determined dermal exposures for the records. It is expected that this definition will be revised in the second version SHEDS-Pesticides under development.

In contrast, SHEDS-PM is designed to address exposures to ambient PM. Thus, the population modeled is defined by their geographic location. Based on information from the MENTOR system (http://www.ccl.rutgers.edu/) the process under development is as follows:

1. Define a study area, a population of interest, appropriate subdivisions of the study area, and an exposure period;
2. Divide the population of interest into an exhaustive set of cohorts;
3. Develop an exposure event sequence for each cohort for the exposure period;
4. Develop estimates of:
    a. The variability of PM concentration in Residential and Non-Residential microenvironments,
    b. Smoking processes and events,
    c. Ventilation rate and physiological indicators associated with each exposure event;
5. Select N representative individuals in the census tract and assign a daily activity diary to each individual based on her/his attributes
6. Obtain random realizations of model parameters specifying Residential, Non-Residential, and Smoking processes and events pertaining to each individual
7. Calculate PM concentrations in Residential, and Non-Residential Microenvironments pertaining to each individual
8. Calculate Total, Outdoor, Residential, and Non-Residential Exposure to PM for each individual
9. Repeat for each of N representative individuals in a census tract
10. Repeat for each census tract

This approach is similar to that used in the NEM models (see Chapter VIII). Complete details on the process and the data used in its development have not been released at this time.

Durations of Time Addressed by the Model

Initial version of SHEDS-Pesticides determines the total dose for periods up to a single day. SHEDS-Pesticides is being revised to model periods with durations of up to one year.

Sources of Exposure Evaluated

SHEDS-Pesticides is limited to pesticides and other dislodgeable compounds present on surfaces in residential environments (SHEDS –Wood). SHEDS-PM is limited to airborne levels of particulates. The sources of particulates are indoor sources, ambient sources, and smoking.

Residential

Residential exposures considered in the initial version SHEDS-Wood are limited to dermal exposure and oral exposures from incidental hand-to-mouth and object-to-mouth.

The SHEDS-Wood relies on CHADS to define the location of the individual in the microenvironments. Data on the distribution of residues on surfaces is supplied by the user.

Diet
A diet model is under development for SHEDS-Pesticides.

Residential Sources of Exposure
SHEDS-Wood is limited to pesticide residues on wood surfaces. SHEDS-Pesticides will include other sources of exposure.

Approach for Addressing Uncertainty
SHED-Pesticides along with TRIM are the only models that attempt to investigate both uncertainty and variability. SHEDS model used the 2-D Monte Carlo modeling (Hoffman and Hammonds, 1994; Price et al. 1996; Zartarian et al. 2000) to define the variability in dose in the simulated population and the uncertainty in the estimates. The sources of uncertainty addressed in the initial version of SHED-pesticides are limited to parameter uncertainty.

"Tool Box" Models

This group of models is composed of separate independent sub-models that can be mixed and matched to solve a wide variety of exposure problems. The "tool box" models have two basic components sub-models and a framework that:

1. Allows the user to define the problem and the relevant sub-models and databases;
2. Allows the use to input additional data;
3. Manages the flow of information between the different sub-models;
4. Manages outputs; and
5. Manages use of platform resources.

By creating a framework of separate models, the programmer is freed to construct internally consistent programs that are not compromised by conflicting need of the other models. In addition, the approach allows the programmer to incorporate existing models. However, the challenge of such models is constructing a framework that will allow models that deal with process that exist on different geographical and temporal scales to work together.

THE LIFELINE GROUP

Modeling ENvironment for Total Risk Assessment (MENTOR)

History and Purpose of the Model

MENTOR is an ongoing modeling project of the Computational Chemodynamics Laboratory of the Environmental and Occupational Health Sciences Institute (jointly sponsored by the Robert Wood Johnson Medical School and Rutgers University).

MENTOR is not a single model; it is an evolving, open, environment for supporting consistent multiscale source-to-dose modeling for human exposures to contaminants. MENTOR has a modular structure with a geographic interface and incorporates (a) libraries of environmental and biological process models (macroenvironmental, ecological/food-web, local multimedia, microenvironmental, activity pattern/exposure event, biological fate and transport, and dose response modules), and (b) libraries of tools to support integrated probabilistic and diagnostic analyses.

The long term goal of MENTOR is to provide state-of-the-art tools for studying the complex and multiscale phenomena that may need to be quantified in order to develop effective control and intervention strategies. Currently MENTOR project is in a research mode and is not planning to release the software for general use in the near future. However, MENTOR will eventually provide an extensible set of ready-to-use methodological tools for performing assessments of exposure/dose for populations or specific individuals, and for a variety of user-defined scenarios.

Platform/Model Design
MENTOR is a Unix program. Individual programs in the MENTOR framework are written in a variety of programming languages. MENTOR is intended to run on high end PCs.

MENTOR is designing and construction a series of models and integrated data bases that will allow the modeling of regional and local sources of atmospheric contaminants (ozone, particulates, and other contaminants), groundwater contamination, indoor airborne contaminants in the residential and occupational environments, exposure that occur as a result point source and non-point source discharges. The goal of MENTOR is to establish a consistent and integrated geographical and temporal framework for multimedia release, fate and transport.

As discussed above MENTOR is linked to the SHEDS model. In this case, SHEDS-PM is viewed as a sub module under the MENTOR system.

What is the Population Modeled?
MENTOR is not designed to model a specific population. Under MENTOR the modeled population can be defined in a wide variety of ways using geographical and demographic criteria.

Durations of Time Addressed by the Model
The various components of Mentor deal with a wide variety of time frames. Periods greater than a year may be considered in ground water models or models of long-term changes in climate. SHEDS-PM in the MENTOR system considers exposure events with durations of five seconds to one year. Indoor air models using computational fluid dynamics may model the movement of contaminants over shorter periods of time.

Sources of Exposure Evaluated
MENTOR has a strong orientation towards the exposure that occur as a result of the movement of contaminates in the environment (national and region air quality, local air quality, widespread or localized contamination ground water.) However, the model framework could be applied to any source of contaminant.

Approach for Addressing Uncertainty
MENTOR can be used to investigate both uncertainty and variation. Because of its design, MENTOR can be used to investigate both scenario, and modeling uncertainty as well as parametric uncertainty.

Total Human Exposure Risk database and Advanced Simulation Environment (THERdbASE)
THERdbASE was developed by EPA's Office of Research and Development (National Exposure Research Laboratory, Las Vegas). THERdbASE is a PC-based computer modeling and database system that contains exposure and risk related information. The system provides a framework for the construction of a suite of exposure- and risk-related models within the Modeling Engine by using information available in data files within the Database Engine. THERdbASE provided a common basis for conducting all residential exposure assessments. THERdbASE married an array of data files with a suite of indoor and outdoor residential and ambient models, and permitted a "cafeteria" approach to selection of data file subsets and models for accomplishing specific modeling activities. Data files included demographic data, food consumption data, physiological data (e.g., distributional data on inhalation rates and body weights), monitoring data on pesticides, and other useful information.

notita™
notita™ is PC-based data model management software[9]. The software is trade secret and the code is not made available. notita™ combines elements of database management, spreadsheet, and statistical analysis software. The model also facilitates simulation programs created under the notitia™ framework. notita™ allows the management of quantitative information that is linked to qualitative information call attributes. Examples of attributes associated with scientific data include specific characterization (e.g., mass and force) and units (e.g., kg and Newton). The ability of a single program to deal with models and data provides a single integrated environment that facilitates the use and management of data and models in an integrated environment.

[9] All information on notita™ is take from the infoscience.com webpage or from personal communications with Dr. Muhilan Pandian.

notitia™ is a user-friendly, graphical, icon-based, modular, Microsoft Windows® software designed by using object-oriented principles. notita™ is written in Visual Basic and is designed to be used on PCs.

Dietary Modeling Projects

Dietary models relate data on the distribution of residues in agricultural crops to the distribution of doses in the general U.S. population. The models are focused on the total U.S. population rather than populations affected by local sources of contamination. Thus, these models will differ from the dietary portion of the waste and air models.

Dietary Exposure Potential Model (DEPM)

The Dietary Exposure Potential Model (DEPM) has been developed by the EPA's Office of Research and Development with support from Exponent, Inc. and Environ Corp. (previously with Technical Assessment Systems, Inc.) over the past five years. The model is a combination of databases that compile information on dietary profiles—consumption of food groups defined from the USDA Continuing Survey of Food Intake by Individuals as well as the FDA's National Health and Nutrition Evaluation Survey. These are summary databases that simplify the use of the information with the functional tools in DEPM that link consumption to contaminant residue information. The model also contains recipe files that build a bridge to agricultural commodities. The model was developed for personal computers with the data files designed in dBASEIV® with FoxPro for Windows® applications programs for queries and reporting. The model is available through the EPA website at www.epa.gov/nerlcwww/depm.htm.

DEPM correlates extant food information in a format for estimating dietary exposure. The resident database system includes several national, government-sponsored food intake surveys and chemical residue monitoring programs. A special feature of the DEPM is the use of recipes developed specifically for exposure analysis that link consumption survey data for prepared foods to the chemical residue information, which is normally reported for raw food ingredients. Consumption in the model is based on 11 food groups containing approximately 800 exposure core food types, established from over 6500 common food items. The summary databases are aggregated in a fashion to allow analyst selection of demographic factors, such age/sex groups, geographical regions, ethnic groups and economic status. Daily intake is estimated by the model for over 300 pesticides and environmental contaminants. In addition, contributions to total exposure from exposure core food groups and individual exposure core foods can also be estimated.

The most recent version of the DEPM has evolved from a process that inventories available food consumption and food residue databases and integrates them in a format conducive for dietary exposure modeling. Several enhancements to the previous version (DEPM V2.3, available since 1996) have been made based on recommendations from exposure scientists. Briefly, the major modifications are:
Improved internal documentation;

- An integrated COMBINE tool, which allows the user to combine residue data from multiple residue databases for specified chemicals and foods;
- A USER-DEFINED DATA tool, which allows the user to incorporate foods or chemicals, and their residues and consumption data, that are not included in the resident databases;
- A TAP WATER option, which allows the user to estimate the contribution of tap water to daily dietary exposure; and
- Resident databases have been upgraded with several new chemicals, and USDA's Pesticide Data Program (PDP) residue data and NHANES III consumption data have been added.

Methodology for Modeling Interindividual Variation in the Population

CEPM relies on the variation in diet reflected in the CSFII.

Durations of Time Addressed by the Model

DEPM focuses on daily exposures.

Approach for Addressing Uncertainty

DEPM focuses on variation in dietary exposures across individuals.

Dietary Exposure and Evaluation Model (DEEM™, and DEEM™-FCID)

The Dietary Exposure and Evaluation Models, DEEM™ and DEEM-FCID™, are a proprietary trade secret software product created by Durango software and licensed by Exponent, Inc. The software is designed to estimate dietary exposures from pesticides used on agricultural commodities. DEEM™ also forms the dietary exposure component of the Calendex™ aggregate and cumulative assessment model. The details of the model were presented to the FIFRA Scientific Advisory Panel at the meeting of February 29 – March 3, 2000 (see, www.epa.gov/scipoly/sap/2000)

Model Architecture
DEEM™ consists of four software modules: the main DEEM™ module, the Acute analysis module, the Chronic analysis module, and the RDFgen™ residue distribution module. The main module facilitates loading and editing chemical-specific residue files. RDFgen™ facilitates the residue distribution adjustments and creates summary statistics and residue distribution files based upon USDA or user-provided data. The Acute analysis and Chronic analysis modules provide dietary exposure assessment models based on USDA CSFII data together with recipe files (translation files) that convert residues in agricultural crops to residues in foods as consumed.

Three types of assessments can be generated with the models available in DEEM™: point estimate, simple distribution and probabilistic assessments using Monte Carlo techniques.

Data Employed by the Model

Data used by the model include:

- Demographic profiles of the individuals in the USDA Continuing Survey of Food Intake by Individuals (CSFII) from the 1989-1992 and the 1994-96 surveys, and the Supplementary Children's Survey of 1998.

- Consumption data from the USDA CSFII studies, described above.

- Weighting factors developed by USDA for these studies. The dietary intake information collected by USDA involves having respondents keep a diary of their food consumption over three days (1989-91) or two non-contiguous days (1994-96). DEEM™ employs records from respondents that completed all days of their survey along with the weighting factors derived by USDA for those records. The weighting factors are designed to adjust the data for non-respondents, and allow combination of data from different years. The weighting factors are designed to make the overall survey records approximate a nationally representative sample of non-institutionalized persons residing in households in the US.

- Proprietary recipe files were initially used with the 1989-91 and 1994-96 CSFII data to convert residues in agricultural crops to residues in foods as eaten. Recently, the recipe files (now called translation files) devised by USDA have been incorporated into DEEM™ along with the 1998 Continuing Survey of Children containing additional demographic and consumption information for children.

- Processing Factors can be applied to the residues on crops as they pass from one form to another along the process of going from the farm to the plate. Processing can increase or decrease the concentration of the pesticide in food items. Default adjustment factors are included in DEEM™. The user may elect to use these data, their own data, or some combination as these files.

- Residue data of several types can be introduced into the model. Single points or distributions (whether empirical or parametric) may be used. Data may be employed representing residues at the point of use of the chemical in the field, or representing the foods at a later stage in the path from farm to plate

- Percent Crop Treated Information Not all chemicals are used on all crops all the time. Data describing the national uses of the chemical on a given crop or crop group may be used to refine the exposure estimate.

- Toxicity Estimates. Toxicity metrics are entered into the model by the user to be employed with the exposure assessment to represent risk. The traditional comparisons are employed: chronic dietary exposures are usually compared to the chronic reference doses (cancer potency factors, chronic NOELs, etc). The acute NOEL can be chosen to represent the toxicity for acute exposure (usually one day or a few days duration of exposure).

Exposure Calculations

There are two types of dietary exposure modules.

The Chronic Module presents the average chronic exposure estimated on a per-capita consumption basis and is compared to the measure of toxicology from lifetime feeding studies. This module uses a point estimate derived for the total US population and 25 subpopulations. They are:

U.S. Population – 48 states, all seasons
Seasonal
Regional
Ethnic
Age and Gender

The Chronic module uses a database of pre-calculated per-capita mean food consumption data (g/kg-bw/day) together with the residue data employed by the user.

The DEEM™ Acute Module computes exposure estimates for the total US population and the subpopulations listed above and six user-specified custom populations defined by age, gender, region, season, nursing status, race and ethnicity.

The DEEM™ acute module combines the food and food form consumption values for each individual in the population of interest with the residue value associated with the food or food form. If the user specified a distribution of residues, the Monte Carlo probability assessment is employed to combine a food consumption value for each individual in the population of interest with a randomly selected value from the distribution of residues.

The Monte Carlo analysis performs a number of iterations (1000 are recommended by the designers), for each user-day. The data generated from these iterations are “binned” or summarized into frequency intervals to simplify the storing and sorting of these observations in subsequent exposure calculations.

Industrial or Waste Disposal Site Models

These models were developed to facilitate the evaluation of exposures from point sources such as specific industrial sites, hazardous-waste sites, and other local sources of

emissions. The models are usually multimedia and multi-route, tracking contaminants through various exposure pathways. However, all the pathways are related back to a single local source. Many of the packages are based on EPA's Risk Assessment Guidance for Superfund Sites (EPA, 1989).

All of the waste models are source based rather than population based. Source based models define the population of interest as the individual actually exposed to a specific product. Such models are difficult to extend to the determination of aggregate and cumulative exposures since there is no connection between the populations defined by different products.

MEPAS

The multimedia environmental pollutant assessment system (MEPAS) was developed by Pacific Northwest Laboratory of Battelle for the U.S. Department of Energy (DOE). MEPAS is a set of codes developed to provide integrated risk information for hazardous, radioactive, and mixed-waste sites. MEPAS couples models of contaminant release, migration, and fate for environmental media with dose rate models based on exposure routes and health consequences for radiological and non-radiological carcinogens and non-carcinogens. Contaminant transport media includes groundwater, overland flow, surface water, air, and food pathways. Human exposure routes include ingestion, inhalation, dermal contact, and external dose. MEPAS provides an overall risk assessment by looking at all pathways and computing aggregate risk to humans from a particular site.

CalTOX

CalTOX was developed to assist the Department of Toxic Substances Control, within the California Environmental Protection Agency, in health risk assessments. It is comprised of a set of spreadsheet models and databases, which can be used to assess human exposure and define soil clean-up levels at uncontrolled hazardous waste sites. The relevant pathways evaluated by CalTOX include contaminated soils and the contamination of adjacent air, surface water, sediments, and ground water. It is composed of various modeling components including a multimedia transport and transformation model, exposure scenario models, and add-ins to quantify and reduce uncertainty and variability. The multimedia transport and transformation model can be used to evaluate time-varying concentrations of contaminants introduced initially into the soil layers and contaminants released continuously into the air or water. CalTOX examines how chemical and landscape properties impact both the ultimate route and quantity of human contact. To estimate average daily potential doses within a human population the multimedia, multiple pathway exposure models are used in the CalTOX model. Twenty-three exposure pathways are contained within the exposure models. In the exposure assessment, contaminant concentrations in the multimedia model compartments are related to contaminant concentrations in the media with which a human population has contact including personal air, tap water, foods, household dusts, and soils.

Platform/Model Design

CalTOX is run using the programs Excel and the Excel add-in program Crystal Ball. The program consists of two linked spreadsheets one models fate and transport the second the dose from exposures.

What is the Population Modeled?

CalTOX is not a population model. The model is defined as the individuals who actually receive exposures from contaminates located at or present

Methodology for Modeling Interindividual Variation in the Population

CalTOX is a source model and defines the model population as those individuals who are exposed to one or more waste-related sources of exposure. The model can evaluate the impact of interindividual variation of input parameters on dose to the exposed individuals.

Durations of Time Addressed by the Model

CalTOX can evaluate long-term exposures (70 years). The model is also designed to track changes in source terms over time.

Sources of Exposure Evaluated

CalTOX evaluates exposures by a large number of pathways including the following: Inhalation, dermal and oral

Inhalation

- Inhalation of gases and particles in outdoor air;
- Inhalation of gases and particles transferred from outdoor air to indoor air;
- Inhalation of soil vapors that migrate to indoor air;
- Inhalation of soil particles transferred to indoor air;
- Indoor inhalation of contaminants transferred from tap water

Ingestion

- Ingestion of fruits, vegetables, and grains contaminated by transfer of atmospheric chemicals to plant tissues;
- Ingestion of meat, milk, and eggs contaminated by transfer of contaminants from air to plants to animals;
- Ingestion of meat, milk, and eggs contaminated through inhalation by animals
- Human soil ingestion;
- Ingestion of fruits, vegetables, and grains contaminated by transfer from soil;
- Ingestion of meat, milk, and eggs contaminated by transfer from soil to plants to animals;

- Ingestion of meat, milk, and eggs contaminated through soil ingestion by animals;
- Ingestion of mother's milk;
- Ingestion of tap water;
- Ingestion of irrigated fruits, vegetables, and grains;
- Ingestion of meat, milk, and eggs from animals consuming contaminated water;
- Ingestion of fish and seafood;
- Ingestion of surface water during swimming or other water recreation;
- Ingestion of mother's milk

Dermal contact

- Dermal contact with soil;
- Dermal contact with tapwater in baths and showers; and
- Dermal contact while swimming.

Approach for Addressing Uncertainty

CalTOX focuses on the exposed individual. Entering distributions into the equations can allow the determination of the variation, uncertainty, or combination of uncertainty and variation in exposure in the population of exposed individuals.

API DSS

History and Purpose of the Model

The American Petroleum Institute Decision Support System (API DSS) was developed to assist environmental professionals in estimating human exposure and risks from contaminated sites. It can be used to approximate site-specific risks, identify the need for site remediation, develop and negotiate site-specific cleanup levels with regulatory agencies, and evaluate the parameter of variability and uncertainty on estimated risk. Four modules make up API DSS Version 2.0 including, the Development of Risk module, the Receptor Point Concentration module, the Chemical Intake and Risk Calculation module, and the Risk Presentation module. The Chemical Intake and Risk Calculation module uses the estimated dose and chemical-specific toxicity to estimate carcinogenic risk and non-carcinogenic hazard index and can be used in either deterministic or Monte Carlo simulation modes. The results of the analysis can be viewed in tabular and graphical format by the Risk Presentation module. The relevant pathways evaluated by the models include vapor intrusion (from soil) into homes, volatilized chemicals from bathroom showers, soil ingestion, and ingestion of food and water.

SmartRISK™

SmartRISK is a trade secret multi-chemical, multi-pathway human health risk assessment modeling program. Pick lists with media, chemicals, and exposure routes are used to build exposure models. SmartRISK uses this information combined with exposure point concentrations and data in user defined default databases to evaluate exposure and

calculate risks. Four different exposure scenarios can be evaluated at one time for reasonable maximum exposed (RME) and alternative exposed populations. All calculations are deterministic. Risk reports created by SmartRISK can be transported to a spreadsheet to perform Monte Carlo Simulation using Crystal Ball or @RISK.

Consumer Product Models

This class of programs has been developed to allow the governments and industry groups the ability to effectively and consistently evaluate exposures to consumers (both residential and occupational end users) from the use of products. The models address a wide range of products and routes of exposure. The models tend to be screening models that attempt to define the reasonable upper bound of exposure from a single or multiple uses of a product.

All of the models are source based rather than population based. Source based models define the population of interest as the individual actually exposed to a specific product. Such models are difficult to extend to the determination of aggregate and cumulative exposures since there is no connection between the populations defined by different products.

E-FAST

E-FAST provides screening-level estimates of the concentrations of chemicals released to air, surface water, landfills, and from consumer products. Estimates provided are potential inhalation, dermal and ingestion dose rates resulting from these releases. Modeled estimates of concentrations and doses are designed to reasonably overestimate exposures, for use in screening level assessment. E-FAST is the modeling successor to a number of consumer models including SEAS, Facsearch (SIDS), PDM3, FLUSH, DERMAL, and SCIES**.**

Platform/Model Design
EFAST is designed to run on PCs using Windows95®, Windows98®, or WindowsNT® operating systems.

What is the Population Modeled?
E-FAST like most consumer models defines the population modeled as the exposed population. The model does not investigate variation in dose in the exposed population or the uncertainty in the estimate.

Durations of Time Addressed by the Model
The basis estimate of exposure is the potential dose received from a single event. Using conservative assumptions for the frequency of events, the model estimates of average dose rate over longer periods of time.

Sources of Exposure Evaluated
E-FAST estimates the levels in the environment associated with the use of the product and the doses that occur from the consumption of tapwater and contaminated fish. The model also estimate a screening level for the potential doses associated with consumer products (the Consumer Exposure Module [CEM]).

Exposure Algorithms
Dermal exposures from consumer products are evaluated using a film-thickness approach. This approach defines the potential dermal dose as the amount contained in a thin film on the skin. The model also evaluates dermal absorption using a permeability coefficient. Inhalation exposure is estimated using a deterministic mass balance calculation. Indoor air in a home is modeled using a two-zone model where the first zone is room where the product is used and the second zone is the remainder of the home. The model does not consider sinks.

Air emissions are modeled using a variety of emission models depending on the exposure scenario chosen.

The model contain as series of pre defined scenarios that facilitate the evaluation of consumer products. These include:

- General Purpose Cleaner (dermal and inhalation)
- Interior Latex Paint (dermal and inhalation)
- Fabric Protector (inhalation)
- Aerosol Paint (inhalation)
- Liquid Laundry Detergent (inhalation)
- Liquid Laundry Detergent (dermal)
- Solid Air Freshener (inhalation)
- Bar Soap (dermal)
- Used Motor Oil (dermal)
- User Defined

Approach for Addressing Uncertainty

E-FAST is intended to product estimates that are conservative with respect to known sources of uncertainty and variation.

CONsumer EXPOsure Model (CONSEXPO-3)

CONSEXPO 3.0 is the most recent version of a multi-route, single-chemical modeling tool for assessing human exposure to chemicals emitted from consumer products. The exposure routes include inhalation, dermal, and oral. For each route of exposure, a number of exposure and uptake models are included.

CONSEXPO is designed to assist in the evaluation of exposure from consumer product. The software includes a number of modeling options that vary from screening models to models that are intended to realistically predict actual exposures and doses. CONSEXPO is based on a modeling framework developed by Van Veen (1995; 1996) to evaluate contact, exposure and uptake of chemicals emitted by consumer products. In this framework, exposure is defined as the concentration of a chemical compound in the medium touching the body. Uptake includes both the intake rate of the contaminated medium and the uptake rate of the compound by the body.

CONSEXPO focuses on non-professional indoor use of consumer products. It provides two tools, algorithms of exposure and a database of model inputs. The models form the core of the program as they provide the exposure and dose estimates. The database is set up to provide input to the models. The database is organized by product categories. After the user selects a product category, the database provides default parameter values to the models.

Platform/Model Design

CONSEXPO 3.0 is a 32-bit application for the Windows® environment (Windows95®, 98, ME, or NT).

Methodology for Modeling Interindividual Variation in the Population

Interindividual variation cannot be modeled in CONSEXPO.

Duration of time addressed by the model

The range of modeling duration allowed by CONSEXPO is not described in its manual.

Dermal Exposures

The doses received from dermal contact are modeled in two steps dermal exposure (or dermal loading) and dermal absorption. The goal of the dermal loading models is to describe the time course of the contaminant at the boundary of the skin that occurs as a result of an exposure event(s).

Because of the wide range of exposures associated with consumer products, there are five dermal loading scenarios defined, and one scenario to model dermal exposure to airborne compounds. The five dermal loading scenarios are:

- Fixed Volume scenario assumes that the product is well mixed;
- Diffusion in Product scenario assumes that the product is not well mixed and transport of a chemical compound takes place by means of diffusion;
- Migration to skin, scenario assumes that dermal exposure as a result of migration of product to the skin;
- Transfer coefficient and contact rate scenarios are similar to the dermal models used in the EPA's residential SOPs.

Note that some of these models require a consideration of dermal absorption as a factor that influences the time course of a contaminant concentration at the skin boundary.

Dermal absorption is model using either a simple "absorbed fraction" or by use of one of two diffusion models. The first diffusion model uses the concentration difference between the product and the blood in the skin. The second an existing model, SKINPERM, makes the simplifying assumption that the concentration in blood is always zero. In both models, the uptake is proportional to the concentration difference, and skin permeability. The skin permeability coefficient can be estimated by any one of six empirical formulas based on the compound's log KOW and the molecular weight.

Non-dietary Oral Exposures

CONSEXPO does not address oral exposure from agricultural sources of contamination. The model does consider exposures that occur from the use of products including certain food-mediated exposures. CONSEXPO has five models of oral exposure from products. These are as follows:

1. Ingestion of products use in and around the mouth (toothpaste, mouth wash, etc.);
2. Ingestion of aerosols or particulates are inhaled and deposited in the nasal-pharyngeal tract;
3. Ingestion of residues by the surface to hand to mouth pathway;
4. Placing objects in the mouth (leaching from product); and
5. Leaching of contaminants into food items that are subsequently consumed (food packaging or containers).

Oral Absorption of ingested contaminants can be modeled based on a simple absorption fraction or by a "tube model of diffusion". The diffusion model can incorporate matrix effects where the contaminant is absorbed as part of a solid.

Approach for Addressing Uncertainty

CONSEXPO has an option that allows the user to input certain input parameters in the form of distributions rather than point estimates, enabling Monte Carlo simulation and sensitivity analysis.

Probabilistic Methodology for Improving Solvent Exposure assessment (PROMISE)

History and Purpose of the Model

PROMISE is an ongoing modeling project by Silken, Inc., for the Solvents Council of the American Chemistry Council. PROMISE Version 8 is available from the American Chemistry Council. The software is owned by Silken, Inc. and is trade secret. PROMISE can be used to calculate multi-route exposures from dermal, inhalation (indoor or outdoors), and/or ingestion routes of solvent exposure. The distribution of the dose can be evaluated and compared for various exposure pathways, alternative exposure and uptake models, and will allow a tiered analysis of exposure.

Platform/Model Design

PROMISE is written FORTRAN and is designed to run on PCs in the Windows® environment (Windows95® and later).

What is the Population Modeled?
PROMISE is not a population model. It defines the individuals modeled as users or residents where a solvent product is being used. PROMISE is a model of the interindividual variation in the doses received in the exposed population. .

Durations of Time Addressed by the Model
PROMISE's focus is the derivation of dose rates that occur over one day to a lifetime. Estimates of exposure that occur over periods longer than one day assume a regular pattern of exposure of one or more exposure events that can be specified by the user. Each type of exposure event in an individual's exposure history is assumed to be identical.

Sources of Exposure Evaluated
The software is designed to evaluate single and multiple uses of products that contain volatile solvents (adhesives, nail polish, paints, floor cleaners, etc.), from activities surrounding the use of large volumes of solvents (open drums or open tanks) or from spills. The model can be used to investigate products used in the workplace and the home.

Exposure Algorithms
PROMISE has algorithms that describe the movement of solvent for an applied product, solvent container, or from a spill. The source models offered in PROMISE are labeled constant concentration, source and ventilation, pure-substance evaporation, "open-can" evaporation, and wall or floor liquid application and evaporation. The program's algorithms model the release of solvent from mixtures that change over time. The model also allows the consideration of the use of multiple products on a surface over time. The equations track the time course of the solvent's concentration in air over time. The model also allows a limited modeling of the receptor' characteristics and how they influence dose. PROMISE includes multiple alternative models for exposure and uptake for each route.

Approach for Addressing Uncertainty
PROMISE makes use of a proprietary Monte Carlo model DISGEN. This model can be used to model variation in dose or the uncertainty in dose depending on the nature of the distribution entered into the model.

Review of Air Models

This class of models seeks to relate exposure that occur from releases of contaminants to air in indoor or outdoor locations.

Simulation Tool Kit for Indoor Air Quality and Inhalation Exposure (IAQX)
IAQX Version 1.0 consists of five stand-alone simulation programs. A general-purpose program performs multi-zone, multi-pollutant simulations and allows gas-phase chemical reactions. Other programs address VOC emissions from solvent-based indoor coating products, small-scale solvent spills, VOC emissions from diffusion-controlled homogeneous slabs, and indoor particulate matter. In addition to performing conventional IAQ simulations, which compute the time-varying concentration profile and inhalation exposure, IAQX can estimate the adequate ventilation rate when certain air quality criteria are provided by the user.

Platform/Model Design
IAQX is a Windows-based simulation software package developed by EPA. The primary outputs of the model are concentration, inhalation exposure, and adequate ventilation rate.

What is the population modeled?
IAQX is intended to model exposure for a single exposure event and a single individual, but can handle multiple contaminants in a single run. There is no modeling of a population.

Methodology for Modeling Interindividual Variation in the Population
Interindividual variation cannot be modeled in IAQX.

Duration of time addressed by the model
The duration of a model run is defined by the user.

Sources of contamination evaluated
IAQX offers a variety of source models that can address emission of chemicals from consumer products, building materials, indoor furnishings, and appliances.

Residential Sources of Exposure
The general-purpose simulation program offers 26 source models as well as 5 sink models and 2 air-filter models. It also allows gas-phase chemical reactions. The source-model groups available in this program include constant and instant sources, first-order and higher-order sources (e.g., exponential decay), solvent evaporation, dry sources, emissions from water, and time-varying indoor sources.

Exposure Algorithms
The manual provided for IAQX does not describe the exposure algorithms.

Inhalation Exposures
As noted above, the IAQX manual does not describe the exposure algorithms. Most likely, the inhalation exposure calculated by the model is a measure of average or time-integrated exposure or dose (e.g., in units of mg/m^3 for exposure or mg for dose).

Approach for Addressing Uncertainty
IAQX has no options for addressing uncertainty.

California Population Indoor Exposure Model (CPIEM)

The California Population Indoor Exposure Model (CPIEM) combines indoor-air concentration distributions with Californians' location/activity profiles to produce exposure/dose distributions for different types of indoor environments. This function is achieved through a Monte Carlo simulation whereby location/activity profiles from prior surveys by the California Air Resources Board are combined with distributions of airborne concentrations for various environments (e.g., residences, schools, office buildings). For many compounds, the concentration data for a given type of environment are either limited or nonexistent. Consequently, the model also has the capability to estimate indoor-air concentration distributions based on distributional information for mass-balance parameters such as emission rates, building volumes and air exchange rates.

Platform/Model Design
CPIEM is written in QuickBASIC for the DOS platform. The primary outputs of the model are summary statistics and accompanying graphs describing the concentration, exposure or dose distribution estimated by the model.

What is the population modeled?

Activity profiles are provided in the model for California adults, adolescents and children.

Methodology for Modeling Interindividual Variation in the Population

For each trial or iteration of the model, an activity profile is sampled from a set of about 3,000 such profiles. The user can select from subgroups of activity profiles defined by factors such as age, gender, primary activity (e.g., work, school, retired), geography and time of year.

Duration of time addressed by the model

The modeling duration for each trial is 24 hours.

Sources of contamination evaluated

As described below, the estimation procedure for indoor-air concentrations in CPIEM is intended to accommodate most types of indoor sources.

Residential Sources of Exposure

Indoor-air concentrations can be modeled in CPIEM for a variety of indoor sources including consumer products, building materials, furnishings and combustion appliances. Sources are categorized in CPIEM as frequent (e.g., tobacco smoking, showering), episodic (e.g., painting, wood burning), and long-term (e.g., range pilot lights, building materials), with a series of input screens keyed to each category.

Exposure Algorithms

The model estimates distributions for inhalation exposure and potential inhaled dose. Inhalation exposure is the time-integrated concentration encountered by an individual while in an indoor environment. Potential inhaled dose is the product of the time-integrated concentration and the individual's breathing rate (i.e., amount of air inhaled per unit time while in the environment).

Inhalation Exposures

The 24-hour, time-integrated inhalation "exposure" in CPIEM is the sum of time-integrated air concentrations encountered by an individual in the course of his/her sequential visits to different environments throughout the day. Within each environment, the time-integrated concentration is simply the product of the sampled (average) air concentration multiplied by the time duration in the environment. Similarly, within each environment the inhalation dose is the product of the concentration times the duration times the breathing rate while in the environment.

Approach for Addressing Uncertainty

Monte Carlo simulation is an integral part of the CPIEM software. The statistical stability of various estimates produced by the model (e.g., mean exposure/dose or various percentiles of the exposure/dose distribution) can be assessed by making repeated model runs with all inputs constant except the user-selectable random number seed.

CONTAM

CONTAM (Dols et. al., 2000) is a computer model developed at the National Institute of Standards and Technology (NIST). CONTAM was originally developed in the 1980's, and the current version, CONTAMW 1.0, is a Windows® based implementation of early versions. CONTAM is a multizone indoor air quality and ventilation model designed to predict contaminant air concentrations and personal exposure resulting from the release of chemicals by a variety of processes.

Platform/Model Design

The current version, CONTAMW 1.0, is a stand-alone program that runs under Windows95/98® or WindowsNT®. Model results can be viewed using built-in charting features for viewing airflows, concentrations and exposures. In addition, the results can be exported to comma delimited data files for import into charting and analysis programs

such as Microsoft Excel. The CONTAM user interface requires the user to supply information about the building components, occupants, weather, and wind profiles.

The most sophisticated capabilities of the model are in the building components definitions and simulation of contaminant emissions and movement. The building component modules allow representation of the following:

- Walls, floors and ceilings, including airflow paths and cracks or leakage areas
- Levels (or floors) of a building
- Zones or volumes of uniform temperature and contaminant concentrations
- Mechanical air-handling equipment, including ducts operating schedules
- Contaminant emission and sink models.

COMTAM also provides models for several special cases of leakage, such as doorways and chimneys, and provides methods for representing duct flow and the operation of fans. Occupant exposure is estimated by providing CONTAM with schedules of locations and breathing rates. Weather and wind effects are represented by schedules. CONTAM then accounts for the effect of wind and temperature on ventilation using fundamental equations for describing temperature and pressure driven airflow across openings in the building envelope.

Modeling Population Exposure

CONTAM is not a population exposure model, and therefore is not ideally suited to estimating population-based exposures. Individual occupant exposure can be estimated by defining individual location and breathing schedules, but variations in the population can only be represented on an individual case basis. The duration of time is user defined, with all inputs such as emission, wind, and occupancy schedules defined over the desired duration.

Emission Models

The available emission models are constant, pressure driven, decaying, and burst release. CONTAM also provides the boundary layer diffusion sink model. These models may be defined in a global manner, representing emissions from building materials, such as emissions from a newly painted room. The user may also define occupant emission rates – or contaminants released by the occupant at the current occupant location.

Exposure Types

CONTAM provides for the estimate of inhalation exposure by using the inhalation rate schedule in combination with predicted air concentrations from model predictions. The model also provides for an inhalation multiplier, a constant multiplier applied to the estimated inhalation exposure, meant to allow the user a means for predicting dose. No models are available for predicting other routes of exposure.

Algorithms

CONTAM solves the system of contaminant mass-balance ordinary differential equations (ODEs) by a user-selected choice of three solution techniques: (1) a direct skyline algorithm; (2) an iterative bi-conjugate gradient algorithm; or (3) an iterative successive over-relaxation algorithm. Contaminant emissions, sinks, pressure, and airflow relationships are described using the appropriate equations within the system ODEs.

The Total Exposure Model (TEM)

The Total Exposure Model (TEM) is a computer model that has been developed with support from the EPA and the US Air Force. The model is a descendent of a model named MAVRIQ (Model for the Analysis of Volatiles and Indoor Air Quality, Wilkes et. al., 1992, Wilkes et. al., 1996). TEM (Wilkes, 1998) is designed to predict the exposure and dose to an individual resulting from use of a contaminated water supply by modeling the fundamental physical and chemical processes that occur during interaction between the contaminated media (in this case water and air) and the exposed individual. The dermal, inhalation, and ingestion calculations are separately maintained to allow a comparison of their respective effects. The integrated model combines emission and fate and transport submodels to estimate resultant human exposure to an individual or population group. The model also estimates body burden (dose to the individual's blood supply). The model also contains an integrated simplified physiologically based pharmacokinetic (PBPK) model and is compatible with a comprehensive PBPK model (ERDEM, Exposure Related Dose Estimating Model). The feasibility of applying TEM to predict exposure and uptake to chloroform based on field data has been demonstrated. (Wilkes and Nuckols, 2000, Lynberg et. al., 2000).

Earlier versions of the model were developed primarily as research tools, but the current version has been developed into a user-friendly tool meant to assist in both population based and individual based exposure assessments. TEM uses Monte Carlo techniques to merge activity pattern data with stochastic or deterministic multiroute exposure models (ingestion, inhalation, and dermal contact) to estimate distributions of exposure of the population to drinking water constituents.

Platform/Model Design

TEM is a stand-alone program developed in C/C++ that runs under Windows95® or later. Model results are stored in an Access database. The model outputs airborne concentrations, personal concentrations, exposures, absorbed dose, and individual target organ concentrations, which can be viewed using built-in charting features. The Access database contains additional detailed information on model inputs, sampled activity patterns, simulated water uses, and other simulation information. In addition, the results can be exported into charting and analysis programs such as Microsoft Excel.

What is the Population Modeled?

TEM is developed to function either as an individual case study model or for estimating population-based exposures. When applied to an individual case study, the user specifies the exact scenario of activities being studied. The model can also be applied in a population mode with user-selected populations and user-defined population characteristics. TEM combines stochastic representation of exposure-related behavior with deterministic calculations of emissions, air concentrations, exposures, and doses. When applied in a population mode, the user specifies the characteristics of each population group as made available by the activity pattern survey. For example, NHAPS provides characteristics such as age, gender, employment, and location in the US. Subsequently, TEM can sample activity patterns from NHAPS meeting the desired characteristics and use the sampled activity patterns as a basis for predicting the distribution of exposures to the specified population. Other input behavioral variables, such as source use behavior may be represented stochastically as a Poisson process for event occurrence and as a lognormal distribution for event duration.

The model implements a number of algorithms to allow stochastic representation of population behavior. The model allows the user to define airflow patterns that respond to user behavior (e.g., when a user takes a shower and the bathroom door is closed, a set of airflows specific to that user behavior may be automatically invoked by the model).

Duration of Time Addressed by the Model

The model simulates the user defined time period for an individual case study and a 24-hour period for a population-based exposure assessment.

Sources of Contamination Evaluated

TEM is designed to represent emissions from a domestic water supply during normal household water uses. As such, TEM is ideally suited for evaluating exposure and dose to any waterborne contaminant. TEM contains a variety of emission models specifically developed to address the release of contaminants from water use appliances in the home. The models are fundamental mass-transfer models developed based on laboratory experiments and the two-film mass transfer theory (Whitman, 1923). Specific water-use emission models are provided in TEM to represent releases from showers, baths, clothes washers, dishwashers, faucets, and toilets. In addition, a generic plug flow model and a completely mixed flow models (CMFM) are provided.

In addition to the emissions specific to waterborne contaminants, TEM also contains general emission models for release of contaminants to the air, including constant, decaying exponential, and burst release. A reversible sink model is also provided.

Ingestion

TEM evaluates exposure and dose to waterborne contaminants that are ingested. Algorithms are provided for stochastically representing ingestion of contaminated drinking water in accordance with user input values for quantity and frequency of

consumption. These parameters are also being analyzed based on information contained in the CSFII data (EPA, 2000b), and these data will be incorporated into the model.

Inhalation

The primary route of exposure for volatile waterborne constituents is the inhalation route. TEM evaluates this exposure by modeling the release of the contaminant during water uses by the aforementioned emission models, the fate and transport of the contaminants, the activities and locations of the occupants, and the physiological and chemical processes leading to uptake into the body. Calculations are preformed utilizing an equilibrium lung model to estimate the mass transferred from the inhaled air into the bloodstream.

Dermal

The dermal exposure and uptake is also estimated based on skin diffusion mass transfer models. The membrane model (Cleek and Bunge, 1993, Wilkes, 1998) is used for estimating the mass transfer across the skin. A simpler, steady state model is also provided (Wilkes, 1998).

Databases

TEM uses databases to provide information necessary for modeling population based exposure behavior. The databases currently linked to TEM or databases used to implement TEM include the following:

> **Ingestion:** The 1994-96 USDA's Continuing Survey of Food Intake by Individuals (CSFII) is the most recent and comprehensive consumption database available. The EPA report, Estimated Per Capita Water Ingestion in the United States (EPA, 2000c), explains the details of the study and presents the results
>
> **Human activity patterns:** National Human Activity Pattern Survey - NHAPS is the largest and most current (1992-1994) human activity pattern data set available. Data for 9386 respondents in the 48 contiguous United States were collected via minute-by-minute 24-hour diaries. Detailed data were collected for a maximum of 82 possible locations and a maximum of 92 activities. In addition, demographic data was collected for each respondent (gender, age, education, week day/weekend, race, census region, race etc.). Advantages of the NHAPS data set are that it is representative of the U.S. population and it has been adjusted to be balanced geographically, seasonally, and for day/time. In addition, it is representative for all ages, gender, and race. This data set has many of the attributes for constructing stochastic activity pattern models (location, duration, frequency) and it is very data rich in water-related activities including taking baths, taking showers, amount of time in the bathroom after bathing or showering, washing of hands, using dishwasher, washing dishes by hand, swimming, etc.
>
> **Water use behavior**: The Residential End Uses of Water Study (REUWS) database contains water use data obtained from 1,188 volunteer households throughout North America (Mayer et. al., 1998). The REUWS study was funded

by the American Water Works Association Research Foundation (AWWARF). During the period from May 1996 through March 1998, approximately 100 single-family detached homes in each of 12 different municipalities (located in California, Colorado, Oregon, Washington, Florida, Arizona, and Ontario) were outfitted with a data-logging device (Meter Master 100 EL, manufactured by Brainard Co., Burlington, NJ) attached to their household water meter (on only magnetic driven water meters). The data logger recorded the water flows at 10-second intervals for a total of four weeks (two in warm weather and two in cool weather) at each household. Following the study, the data was retrieved and analyzed by a flow trace analysis software program, called Trace Wizard, developed by Aquacraft, Inc., Boulder, CO, which disaggregated the total flows into individual end uses (i.e. toilet, shower, faucet, dishwasher, clothes washer, etc) (Mayer et al. 1998). In addition to identifying the type of water use (e.g. shower, faucet, toilet), Trace Wizard identified the event durations, volumes, peak flows, and mode measurements for each water-using event.

The Residential Energy Consumption Survey (RECS) was a nationwide survey conducted in 1997 to obtain household energy use information. The resultant RECS database contains energy usage characteristics of 5,900 residential housing units. The information was acquired through on-site personal interviews with residents; telephone interviews with rental agents of units where energy use was included in the rent; and mail questionnaires to energy suppliers to the units. The database contains information on physical characteristics of the housing units, demographic information of the residents, heating and cooling appliances used, clothes washer and dishwasher use frequency information, fuel types, and energy consumption.

Approach for Addressing Uncertainty

TEM is developed to address variability, and as such contains the ability to define many activities in terms of distributions and frequencies. Many of these capabilities are readily adaptable to addressing uncertainty.

Multi-Chamber Concentration and Exposure Model (MCCEM)

The Multi-Chamber Concentration and Exposure Model (MCCEM) is a user-friendly computer program that estimates indoor concentrations for, and inhalation exposure to, chemicals released from products or materials used in a residence. For each model run, time-varying indoor-air concentrations and inhalation exposure are modeled for one chemical in as many as four zones (chambers) of a residence. One exposure event (e.g., one episode of use of a consumer product) typically is modeled, from which single-event and lifetime exposure estimates are developed based on user inputs.

Platform/Model Design

MCCEM is written entirely in C++ and is a stand-alone program that runs on Windows 95 (and later versions of Windows). The primary output of the model is a set of exposure measures (e.g., peak concentration, single-event dose, LADC, LADD) relating to the exposure event that has been modeled. For lifetime exposure measures such as LADC and LADD, it is assumed that the modeled exposure event occurs repeatedly throughout an individual's lifetime, at a frequency specified by the user. A time-series of indoor-air concentrations in each zone also is output from the model, in a format that can be imported readily into spreadsheet software such as Excel.

What is the population modeled?

MCCEM is intended to model exposure for a single exposure event and a single individual. There is no modeling of a population.

Methodology for Modeling Interindividual Variation in the Population

Interindividual variation cannot be modeled in MCCEM.

Duration of time addressed by the model

The typical modeling duration for MCCEM ranges from one day to one year.

Sources of contamination evaluated

MCCEM is intended to support EPA/OPPT in assessing inhalation exposures to new and existing chemicals in consumer products, building materials, or indoor furnishings.

Residential Sources of Exposure
MCCEM focuses on consumer products, building materials, and indoor furnishings as sources of exposure. The user can choose from several types of pre-formatted emission profiles for these sources, or can enter time-varying emission rates explicitly or import them from an ASCII file. The four types of source models available in MCCEM are constant, single exponential, incremental and data entry. MCCEM currently does not include complex source models such as those for aerosols (e.g., to treat coagulation of particles in the air and subsequent size-dependent particle deposition rates), but can account for reversible and irreversible indoor sinks.

Approach for Addressing Uncertainty

MCCEM has a Monte Carlo option that allows the user to develop a range of exposure estimates by making multiple runs while varying one or more of the following parameters – infiltration rate, emission rate or sink rate – about the values entered on other input screens. With this option, each input parameter chosen by the user is treated in the form of a distribution, with a central value that represents the user's input on the corresponding

screen. Four types of distributions are available for each input parameter – uniform, normal, triangular and lognormal. When Monte Carlo simulation is used, the output from MCCEM is restricted to summary statistics (e.g., peak concentration, LADC) for each trial.

Relevance to Comprehensive Chemical Exposure Framework

Some of the algorithms and calculation routines in MCCEM, such as those pertaining to source and sink models, may be useful for calculating indoor-air concentrations and inhalation exposures within the framework.

RISK

Background /History

RISK is the third in a series of indoor air quality models developed by the Indoor Environment Management Branch of the EPA National Risk Management Research Laboratory. The first model, INDOOR, was designed to calculate the indoor pollutant concentrations from indoor sources. The second model, EXPOSURE, extended INDOOR to allow calculation of individual exposure. RISK extends EXPOSURE to allow analysis of individual risk to indoor pollutant sources. The three models were all developed as tools to carry out the mission of the engineering portion of the EPA's indoor air research program "To provide tools necessary to reduce individual exposure and risk to indoor air pollutants."

Platform/Model Design

RISK was designed using the concepts of buildings and scenarios. The fixed information about a building, number of rooms, room dimensions, and arrangement of the rooms is contained in a building file. The changing information – sources, sinks, air exchange, room-to-room flows, etc. – is contained in scenario files. The steps in using the model are: (1) define the building; (2) save the building information to a file; (3) define the scenario; (4) save the scenario to disk; and (5) run the model. RISK provides a wide range of graphical and tabular outputs of the results of the calculations. Summary outputs of risk and exposure are provided in tabular form. Full risk, exposure, and concentration outputs are also provided in tabular form. The tabular output is supplemented by graphs of concentration and exposure versus time. The calculated results can also be saved to disk for later analysis.

What is the population modeled?

RISK is intended to model exposure for a single exposure event and a single individual. There is no modeling of a population.

Methodology for Modeling Interindividual Variation in the Population

Interindividual variation cannot be modeled in RISK.

Duration of time addressed by the model

RISK can model durations ranging from one day or shorter to multiple years.

Sources of contamination evaluated

RISK provides source models that can be applied to consumer products, building materials, indoor furnishings and appliances burning fossil fuels.

Residential Sources of Exposure

As noted above, RISK can accommodate sources such as consumer products, building materials, indoor furnishings and appliances. Source models available in RISK include exponential decay models, mass transfer models, empirical models for latex paint, and on/off (constant emission rate when on) models. The model also can account for reversible and irreversible indoor sinks.

Approach for Addressing Uncertainty

RISK has no options for addressing uncertainty.

Total Risk Integrated Methodology (TRIM)

TRIM is an ongoing modeling project of EPA's Office of Air Quality Planning and Standards. The program is intended to support OAQPS action under the Clean Air Act (CAA). They include the residual risk program, delisting petitions, and the establishment of national ambient air quality standards. Air emissions can result in exposures by multiple pathways, oral and dermal, as well as inhalation. As a result, TRIM has been designed to evaluate the aggregate exposures to a single compound that occur as the result of the releases of that compound to air. The concern for risks from air pollutants ranges for acute exposures to lifetime average exposures; therefore, TRIM will evaluate exposures that occur over a wide range of durations. The model also has to be able to track the exposure and resulting dose back to sources regulated under the CAA. Therefore, TRIM is being designed to link a longitudinal aggregate exposures model to a fate and transport model.

The model is being developed in phases. APEX is one of the exposure models that are being designed for use within TRIM.Expo. The Air Pollutants Exposure model (APEX(3.0)) is a PC-based model that was derived from the probabilistic NAAQS Exposure Model for carbon monoxide (pNEM/CO). The model simulates the movement of individuals through time and space and their exposure to the given pollutant in indoor, outdoor, and in-vehicle microenvironments. Several features of the model have been made flexible so that various gaseous pollutants can be analyzed by inputting appropriate

pollutant-specific information. The user may choose the number and types of microenvironments to be included, select the time period of interest, use either monitored ambient data or values provided from dispersion or other modeling runs, and use either a mass balance approach or an empirical ratio-based (factor) approach to estimate indoor or in-vehicle concentrations.

The main exposure program stochastically generates simulated individuals using census-derived probability distributions for the demographic variables. Each such individual is assigned a series of time-activity diaries that are matched on the day type, temperature, age, gender, employment status, and optionally on other variables. The model then estimates the sequence of pollutant exposures for that individual, along with inhaled dose. Any number of simulated individuals can be modeled, and collectively they represent a random sample of the study area population.

Platform/Model Design

TRIM is being designed as a modular program designed to be run on PCs.

TRIM.fate is designed to relate air emissions sources in specific geographic locations to levels of contaminants in air food and water at specific locations in the U.S. TRIM.expo is a longitudinal model of aggregate exposures to individuals and cohorts. TRIM.risk combine toxicity data and the output of TRIM.expo.

APEX works in the Multimedia Integrated Modeling System (MIMS) framework was designed and developed by the EPA Office of Research and Development. MIMS helps a user configure sets of models that can work together, sharing input and output files. The MIMS framework is designed to integrate models of different media (e.g., atmosphere, land basin, surface water basin, macrobiota, subsurface) into a single software package. It supports the study of an entire ecosystem. MIMS also supports complex computational studies that use multiple interrelated models / programs, such as the modules within TRIM.

What is the Population Modeled?

TRIM has a strong geographic orientation that results from the need to relate exposure and risk back to specific emission sources at specific locations. Thus, the model focuses on geographically defined study areas (census tracts, or other areas). Larger areas are built up from these units. Using this approach, the entire U.S. can be studied.

Inside the units the population can be divided based on a wide variety of demographic factors. TRIM relies on groups of individuals called cohorts, which are treated as having similar exposures.

Durations of Time Addressed by the Model

TRIM is designed to estimate exposures for all time periods from less than a day to the average dose across a lifetime.

Sources of Exposure Evaluated

TRIM is still under development thus the specific pathways that will be address in future versions are uncertain. Pathways that are under consideration include the following:

- Inhalation out of doors (ambient air levels);
- Inhalation in microenvironments (indoors, vehicles, workplaces, institutions, etc.);
- Consumption of fish;
- Tapwater consumption;
- Ingestion of soil and house dust;
- Non-ingestion tapwater pathways;
- Consumption of locally produced meat and dairy products, and
- Consumption of locally grown agricultural commodities.

In all of the pathways, the emphasis is on how these routes of exposure could be affected by release of contaminants to air. (These pathways are addressed in TRIM.fate.)
The exposures are evaluated using an "event" model. An event could be inhalation in a microenvironment or the consumption of a food item. Activity pattern data are used to define the events in a person's life. TRIM will be based on the CHADS database.

Approach for Addressing Uncertainty

TRIM will separately model uncertainty and variation. Details on how this will be done have not been released for TRIM.expo.

Indirect Models

The models described below are not indoor-air models per se. Rather, they share a common feature in that total (24-hour) exposure distributions can be developed by combining distributions for microenvironment-specific concentrations with information on population activity patterns, or time spent in each microenvironment by individuals. Nearly all of these models involve use of Monte Carlo simulation techniques and were originally developed to estimate population exposures to airborne contaminants in outdoor air. Some have evolved to the point of including mass-balance routines to simulate concentration distributions for indoor environments.

The table below summarizes selected features of the following models:

- AirPEX (Air Pollution Exposure Model);
- BEAM (Benzene Exposure Assessment Model);
- HEM (Human Exposure Model;
- pHAP (probabilistic Hazardous Air Pollutant exposure model);
- pNEM (probabilistic NAAQS Exposure Model);
- SHAPE (Simulation of Human Activities and Pollutant Exposure);
- SHEDS (Stochastic Human Exposure and Dose Simulation);

- HAPEM (Hazardous Air Pollutant Exposure Model); and
- SCREAM (South Coast Risk and Exposure Assessment Model).

As summarized in the table, some of the models use a simplistic approach such as indoor/outdoor (I/O) ratios to estimate indoor-air concentrations whereas others use a mass-balance framework. The latter may have some features or concepts of use for the Framework.

Model	**Contaminants**	**Estimation of Indoor-air Concentrations**
AirPEX	Benzene, B(a)P, ozone, PM	I/O ratios
BEAM	Benzene	
HEM	Toxic air pollutants	I/O ratios
PHAP	Hazardous air pollutants	
PNEM	O_3, CO, PM	Mass-balance model
SHAPE	CO	
SHEDS	Pesticides, PM	Empirical mass-balance model (regression)
HAPEM	Hazardous air pollutants	Penetration factors
SCREAM	Air toxics	I/O ratios, mass-balance model

Occupational Models

Very few models of workplace exposures were identified in the phase of the project. Workplace risk assessments are driven by monitoring based industrial hygiene and product stewardship programs rather than by modeling. The three models were identified "The Jayjock ToolKit", ChemSTEER, and EASE.

Dr. Michael Jayjock has assembled a set of mass balance models of air concentrations using simple DOS programs and Excel spreadsheets.

Chemical Screening Tool For Exposures & Environmental Releases (ChemSTEER) was developed by EPA's Office of Pollution Prevention and Toxics as part of the PMN process. Like E-Fast, the goal of ChemSTEER is to take minimal data and use simple mass balance equations to derive estimates of reasonable conservative workplace exposures.

EASE developed by the UK by the Health and Safety Executive. EASE is a database of airborne measurements of a wide variety of gasses, vapors, and dusts taken from various sources. The data are sorted by the physical characteristics of the compound and details of the industrial processes where the measurements are taken. The user is queried on the nature of the process and the compound. Based on the user's responses, the model

selects the airborne concentrations in the database that are associated with similar compounds and conditions.
The EASE computer model was developed in the Europe to assist exposure assessment for both new and existing substances. The model can be used to predict exposure by both inhalation and dermal contact using task and situation specific information about the substance and methods of control.

Discussion

Based on this review of current modeling the field of exposure modeling is in great ferment. A number of organizations are seeing to grapple with the problems of:

- Performing aggregate and cumulative risk;
- Modeling exposures from diverse sources;
- Developing efficient but accurate models of emissions and sinks in indoor air models;
- Determining doses for various time periods; and
- Longitudinal modeling with only short-term data on activity patterns.

This has led to multiple projects with similar goals and approaches. The FQPA-driven projects have the lead on the integration of diet, water, and residential dermal exposures but do not address exposures from contaminant in ambient air that occur from local or regional sources or from occupational exposures. The MENTOR and TRIM programs have strong abilities in the areas of geographical modeling. The waste models provide examples of integration of multi-route exposures but are limited to those pathways affected by solid and hazardous wastes (soil, ground water, ambient air).

Data on models of occupational exposure from the use of products is minimal. While the issue of intraindividual variation in occupational exposure has been the subject of several publications (Francis et al., 1989; Nicas and Spear, 1993a,b), no models of longitudinal occupational exposures (event based) have been identified.

On the positive side, the basic framework for evaluating dermal and inhalation exposures and doses to consumer chemicals appears to be in place in models like CONSEXPO, IAQX, TEM, and in the research performed under FQPA. These models will allow the doses to be reasonably predicted from consumer products.

The task of modeling individuals' exposure-related characteristics has also been explored by several of the modeling groups. The models include data from a number of national and local surveys of exposure related information. Table 2 presents a listing of the surveys and the organizations that have created them.

A major data gap in this modeling effort is the lack of data on frequency of usage and the correlation of usage to factors that influence exposure, room sizes, ventilation rates, and presence of children during and following usage.

Table 2. Databases Incorporated in Models

Continuing Survey of Food Intakes by Individuals, 1989-1991.
Agricultural Research Service, Beltsville Human Nutrition Research Center, Food Surveys Research Group, US Department of Agriculture, 1991.

Continuing Survey of Food Intake by Individuals, 1994-96; Supplemental Children's Survey, 1998
Agricultural Research Service, Beltsville Human Nutrition Research Center, Food Surveys Research Group, US Department of Agriculture.

Current Population Survey, Annual Demographic Survey - March Supplement, 1992-1994 and 1996-1999 Data Sets.
Bureau of the Census, US Department of Commerce, and Bureau of Labor Statistics, US Department of Labor, 1999.

"Census of Population and Housing, 1990: Public Use Microdata Samples/
Bureau of the Census, 1992.

American Housing Survey.
Bureau of the Census and US Department of Housing and Urban Development, 1993

1996 Natality Data Set
National Center for Health Statistics, Centers for Disease Control and Prevention, U.S. Department of Health and Human Services, 1996.

National Health and Nutrition Examination Survey (NHANES III)
National Center for Health Statistics, 1994. *1988-1994*

National Home and Garden Pesticide Use Survey.
EPA, 1992b. Prepared by the Research Triangle Institute for the Office of Pesticides and Toxic Substances, Biological and Economic Analysis Branch.

National Human Activity Pattern Survey.
EPA, 1994. Human Exposure and Atmospheric Sciences Division, Human Exposure Research Branch,

National Home and Garden Pesticide Use Survey
EPA, 1992b. Prepared by the Research Triangle Institute for the Office of Pesticides and Toxic Substances, Biological and Economic Analysis Branch.

Consolidated Human Activities Database (CHAD)
EPA, 2000. Office or Research and Development, National Exposure Research Lab, Human Exposure and Atmospheric Sciences Division

Residential End Uses of Water Study (REUWS)
American Water Works Association Research Foundation.

Residential Energy Consumption Survey (RECS)

Chapter 3. Design for the Comprehensive Chemical Exposure Framework

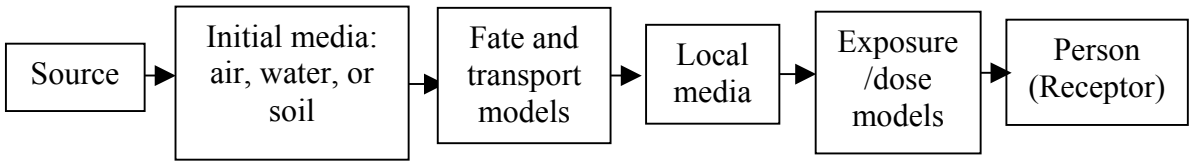
This section presents the projects team's proposed approach for the Framework. The section begins with the presentation of a discussion of the limitations of source-to-dose models[10] and the concept of person-oriented modeling (POM). The components of the Framework are then presented in a systematic manner; technical issues are discussed, and a modular design for a computer program that could implement the Framework is presented.

Proposed Approach: Person-Oriented Modeling (POM)

The challenge of designing a single Framework for characterizing concurrent exposures to widely different sources of multiple chemicals leads inexorably to a person- or receptor-oriented designs (CLA, 2000; Zartarian 2000; Muir et al., 1997; Price et al., 1996). Person-oriented modeling (POM) designs are not a new concept and have been used in a number of software programs developed by a variety of researchers. The approach, however, has not been clearly described in the literature. POM begins with a focus on the population of persons rather than chemicals or sources. To understand this difference it is useful to review the paradigm that historically has governed most exposure assessments and most exposure software - source-to-dose modeling.

Source-to-dose models provide the basis for historical exposure assessment and much of EPA's current exposure research[11]. The design of a source-to-dose model is given in Figure 1. The components of such a model are as follows.

Figure 1. Source-to-Dose Models



[10] In this report, the term model is used to refer to conceptual models or in some cases simple algorithms of dose. The term software models will refer to actual computer programs.
[11] See for example EPA's Human Exposure Source-to-Dose Modeling (HES2D) project http://www.epa.gov/heasd/emrb/emrb.htm.

Source. The source is defined as a function of specific process and may have a strong geographic component[12]. The source typically is where chemicals of concern enter the environment. Example of sources include smoke stacks, discharge pipes for wastewater, hazardous waste units, tail pipes of vehicles. The source also is the point at which regulatory decisions (to control or not to control) are usually made.

Initial media. These are the air, water and soil adjacent to the source that directly receive the chemicals of concern.

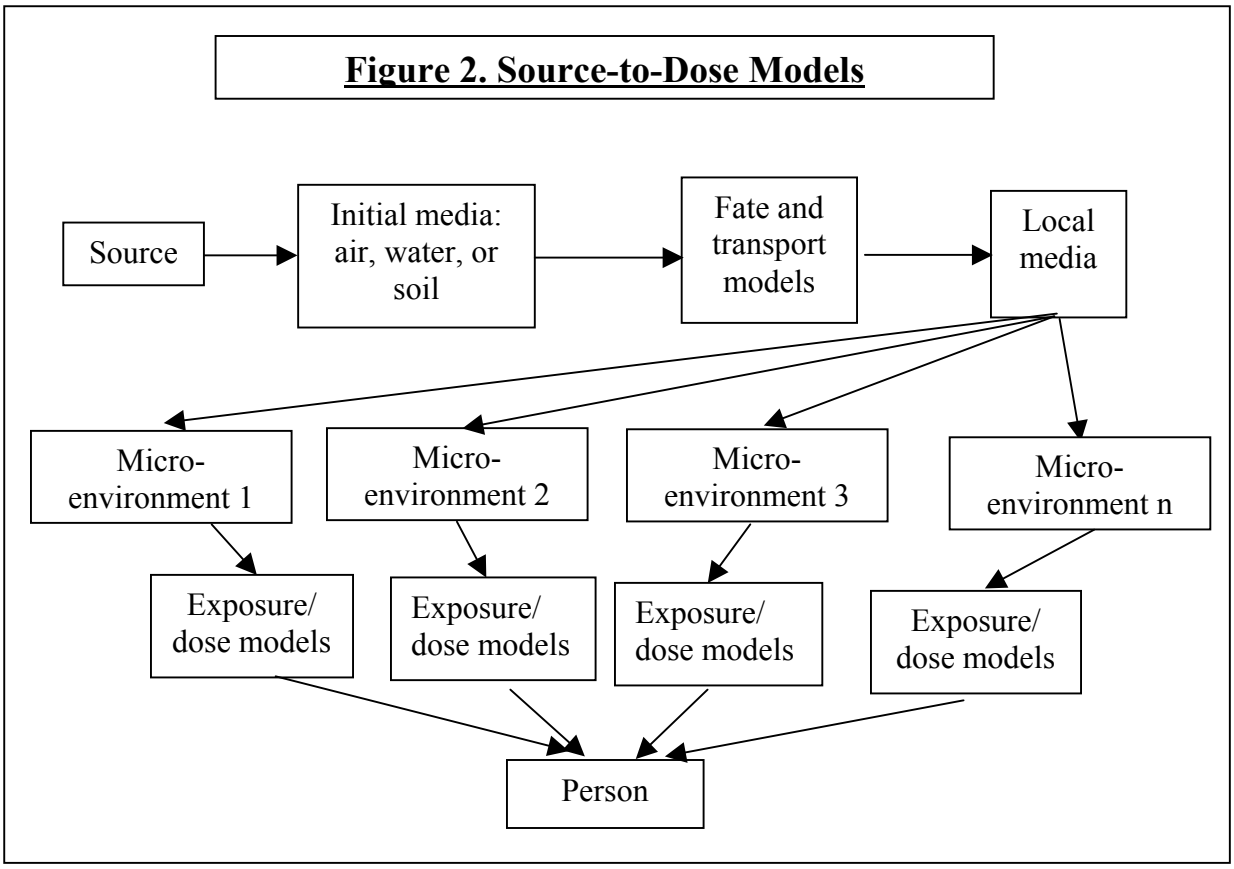
Fate and transport models. These models capture the impact of the physical and chemical processes that occur as a chemical moves from the point of release to the media with which the receptor comes into contact.

Exposure and dose models. These models determine how the person's characteristics (behaviors and physiology) determine the concentrations of the chemical at the person's boundaries over time (exposures) and the rates at which the chemicals of concern that enter the person (dose).

Person. The person (or receptor) consists of a set of characteristics or properties. This can be a single set of values for a hypothetical person (such as the typical person, reasonable maximally exposed person, or theoretical upper bound person) or sets of persons whose differences reflect inter-individual variation of characteristics across a population or the uncertainty in the estimates of the characteristics or both. The population in source-to-dose models is typically defined as those receiving a dose from the source (the exposed persons or population at risk).

Source-to-dose models can be made more complex if the person is modeled as having multiple routes of exposures to a source in multiple microenvironments, see Figure 2. In these models, the person's characteristics are extended to include activity patterns.

[12] Sources include both point sources that have specific locations, area sources (e.g. tailpipe emissions or urban run off), or can be defined without regard to location (e.g. exposures that happen from consumer products or from diet).



Source-to-dose models have been used in regulations that set emission standards under the Clean Water and Clean Air Acts, clean up standards for hazardous waste sites, and tolerances for chemical additives in food. The widespread use of these models occurs for two reasons. First, regulatory agencies place a high priority in defining the relationship between a specific source and the resulting doses in the affected population. The reason for this focus is that the majority of regulatory programs address specific sources of exposure (drinking water, surface waters, waste sites, air emissions, diet, and residential exposures). Thus, the risk management question is "What are the risks posed by a chemical from a specific source?" Source-to-dose models supply this information.

Second, by following a chemical from a source to a final dose the researcher is forced to systematically address all of the processes that determine the movement of a chemical from the source to the exposed person. Models of each step in the process can be linked so that the output of the model of one portion of the process becomes the input of the model for the next portion. This allow the creation of overarching models such as the MENTOR project[13] that can explore the cumulative impact of uncertainty and variation in doses in exposed populations that are caused by a certain source.

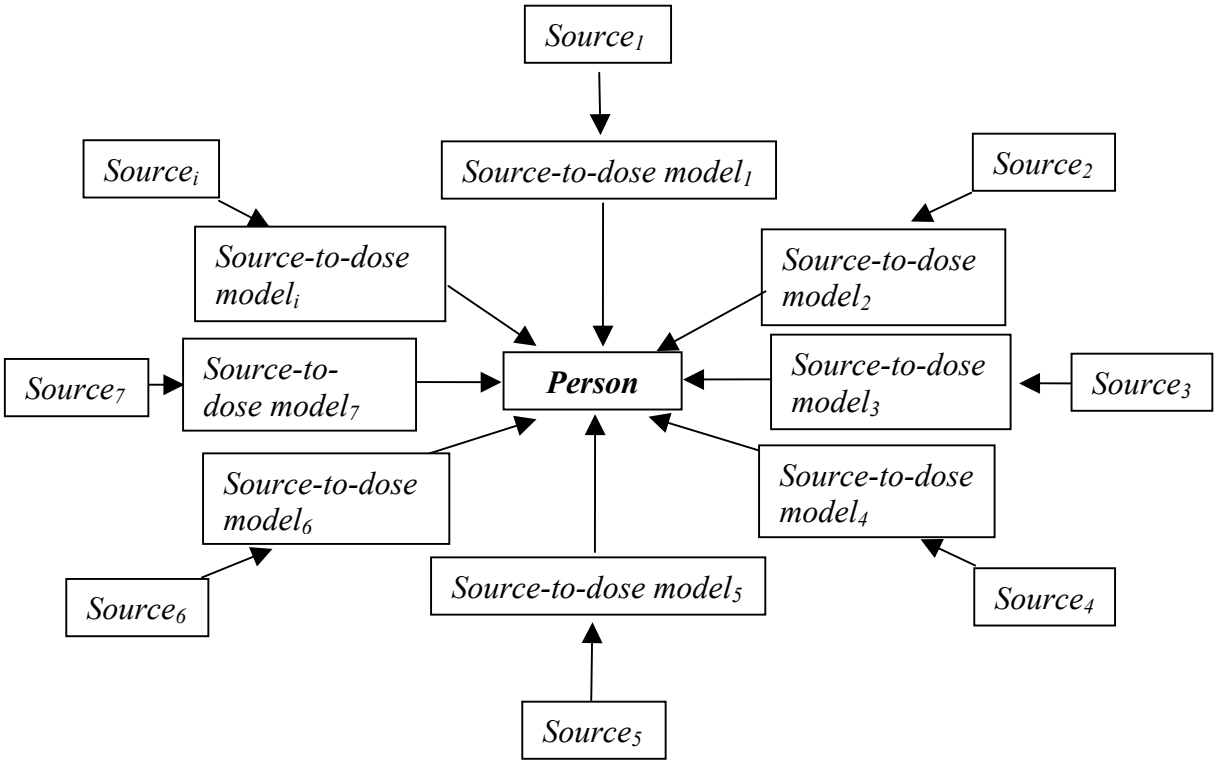
The weakness of this approach is that the resulting exposure models are based on the characteristics of the specific sources of the exposure. The sources' characteristics define

[13] For information on this project see, http://www.ccl.rutgers.edu/

the beginning point of the model and influence the design of all subsequent portions of the model. Fate and transport models only deal with the media through which the source's contaminants pass. The microenvironments that are included are only those relevant to the source and contaminant. Finally, the population modeled consists only of those persons who receive a dose of the chemical of interest from the source. This of course makes sense if one has a mandate to specifically address the impacts of a single source; why include models of processes not relevant to the chemical and why dilute the affected population with persons not affected by the source?

This dominance of the model by the source; however, causes problems when the goal of the modeling is to determine the total exposure to a chemical or group of chemicals. This is generally a better model of industrial, chemical, and demographic realities[14], if not of legislative mandates. Models of total exposures for many chemicals must address multiple independent sources of exposure, each with independent source to dose models, see Figure 3.

Figure 3. Multi-Source Exposure Modeling



In the determination of total exposures, the population of concern is defined by multiple sources of exposure and may or may not fit with the populations defined by the individual sources. In addition, when modeling total exposures in a population, the

[14] Acetone provides an example of a chemical with multiple sources (ATSDR, 1994) including occupational, consumer products, indoor and ambient air; food; and endogenous production.

models must determine which sources of exposure apply to each person in the population and which do not. Finally, the use of multiple models creates a need for consistency across the different source-to-dose models. If two source-to-dose models predict a chemical concentration in a microenvironment, such as a back yard, and one model assigns the person to an urban town house with a small yard and the second assigns the person to a rural home with a large yard, then the prediction of the total dose is not likely to be a realistic reflection of an actual person. Similar problems can occur with assumptions concerning the person's age, weight, or the season when the exposure occurs. EPA in its guidance for aggregate exposure assessments calls this the need for consistency in the temporal, spatial, and demographic characteristics of persons within the population (EPA, 2000a).

The need for consistency of assumptions for the characteristics of the modeled person and the need to determine which source applies to a modeled person leads to the development of person-centered model designs for multi-source models and moves the sources to the periphery of the model design.

Designing the Framework Using POM

As discussed above, the concept of POM is not a new idea. The majority of the microexposure models BEAM, SHAPE, and THERdbASE and the aggregate models developed for FQPA, CARES™ (CLA, 2002), LifeLine™ (Muir et al., 1997) Calendex™ (Novigen, 2000), and SHEDS (EPA, 2002) are person-oriented models; however, the defining characteristics of POM have not been well described in the literature. In this section, we develop a Framework using POM. This section will outline the processes and will provide examples to illustrate various points. However, this section will not discuss whether data necessary to construct actual models exist or how such models would be developed. That discussion will occur in later sections of this chapter.

Modeling Doses from Multiple Sources

The basic form of POM is relatively simple. A POM design begins the modeling process by defining the exposure-related characteristics of the person being modeled[15]. This definition requires the modeler and the exposure assessor to clearly define the population of interest. This is not a trivial task and will involve the consideration of the nature of the decisions the exposure assessment will support. Defining the modeled population is discussed later in this chapter.

[15] The Framework addresses the variation of total dose to one or more chemicals across a population. Therefore, the approach will not address the hypothetical individuals used in deterministic exposure assessments such are the RME (reasonable maximum exposed individual), MEI (maximally exposed individual), TUBE (Theoretical upper bound exposed individual), or "typical" individual.

Based on the definition of the population, the characteristics of a person[16] that are relevant to the assessment are defined. Using these characteristics, the model then determines the probability of being exposed to a specific source on a given day and, if exposed, the resulting doses. This process is repeated for the next person in the population. Thus, while exposure-to-dose models use the source to define the model structure, POMs use the nature of the population of interest to define the model structure.

Figure 4 presents a flow chart for simple model of exposures to a single chemical from multiple sources that occur during a single time period. A time period is defined as a duration of time sufficiently short that:

1. The sum of the doses can be treated as a single dose for the purpose of evaluating risk; and
2. The person's exposure-related characteristics (breathing rates, tapwater consumption, location, etc.) can be treated as constants.

This duration may be as short as a few seconds, or as long as a year, depending on the source of exposure (Price et al. 1997).

The initial step of the model is to assign the person's exposure-related characteristics. Once the person's characteristics are assigned, the model enters a loop (exposure event loop). In the exposure event loop, the model sequentially evaluates each source of the person's exposures[17].

The determination of whether an exposure to a given source occurs is conditional on the person's characteristics. For example, if a person is two years old there is a higher chance that she or he will have an oral exposure to a phthalate plasticizer used in toys than if she or he is 25 years old. Women are more likely to have acetone exposure from use of nail products then men. This ability to make conditional decisions on whether a person is exposed to a specific source is an essential characteristic of POMs.

[16] A person may be based on data taken from a single person or data from multiple individuals from multiple surveys. However, in either case the intent is to model the exposure received by a hypothetical but representative individual for the population of interest not the historical person who participated in a survey.

[17] Conceptually, this need not be a loop if the software is implemented in parallel architecture. However, such an approach would require that the number and nature of exposure sources be hardwired into the model

The decision of whether a person is exposed is made independently for each source. This allows the assessor to model when exposures to different sources will and will not co-occur. For example, a modeler may wish to assume that person who rides a bus to work on a given day will not commute in a car. Thus, in an assessment of benzene exposure, the determination of benzene exposures from commuting in a car versus in a bus can be set up as mutually exclusive[18]. Where the exposures are associated with one another the decision that one exposure occurs can be linked to a second source. Thus, a glycol ether exposure from a floor stripper (wax remover) can be linked to an exposure from a subsequent application of a floor wax. The development of the conditional probabilities for the occurrence of an exposure is discussed below.

Once the decision has been made that the person has been exposed to a source, then a source-to-dose model is used to determine the dose. However, now the source-to-dose model is tailored to the characteristics of the person. This allows the model to maintain consistency in the assumptions for the modeled person across multiple source-to-dose models. The doses from the source may occur by multiple routes (oral, dermal, and inhalation) or a single route. These route-specific doses are stored for later analysis. If the exposure to a source does not occur, then the model proceeds to the next source. This process is repeated until all sources of exposure are evaluated.

Once the sources are evaluated, the total doses from each source can be summed to give total route-specific doses for the time step. The doses can also be segregated by source to give the source-specific doses. The possible outputs from this analysis of one person are a set of route- and source- specific doses and the total dose. These route-specific doses can be used as:

1. Inputs to route-specific risk characterization models (using oral, inhalation and dermal RfDs);

Figure 3. Person-Based Exposure Modeling

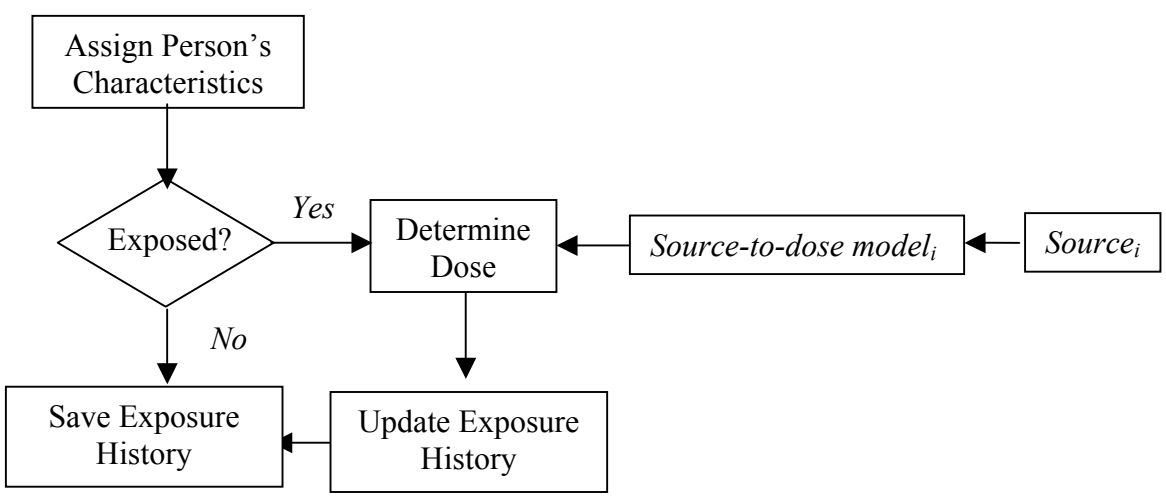
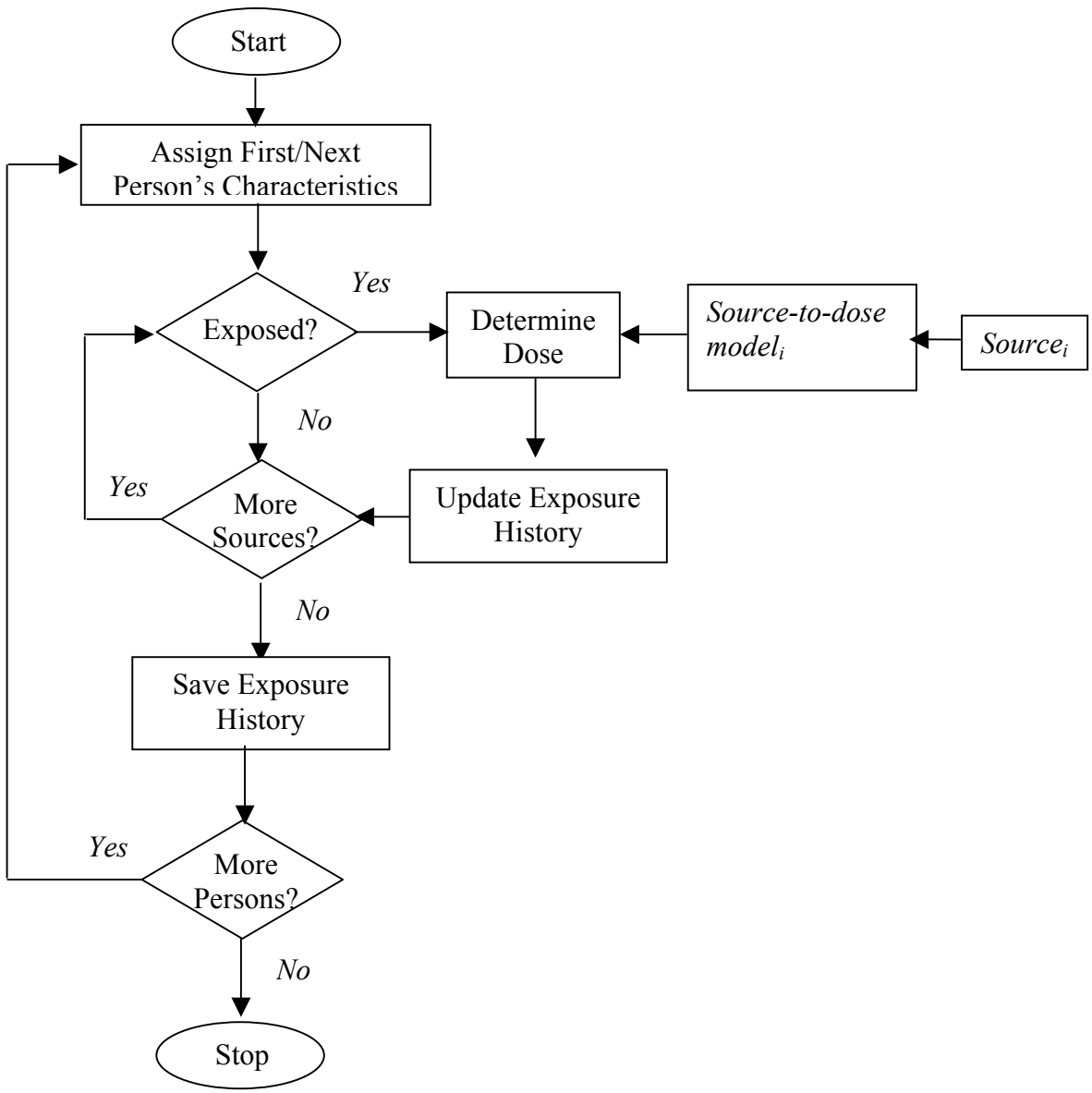


Figure 5. Person-Based Modeling of Inter-individual Variation in Dose-One Time Step



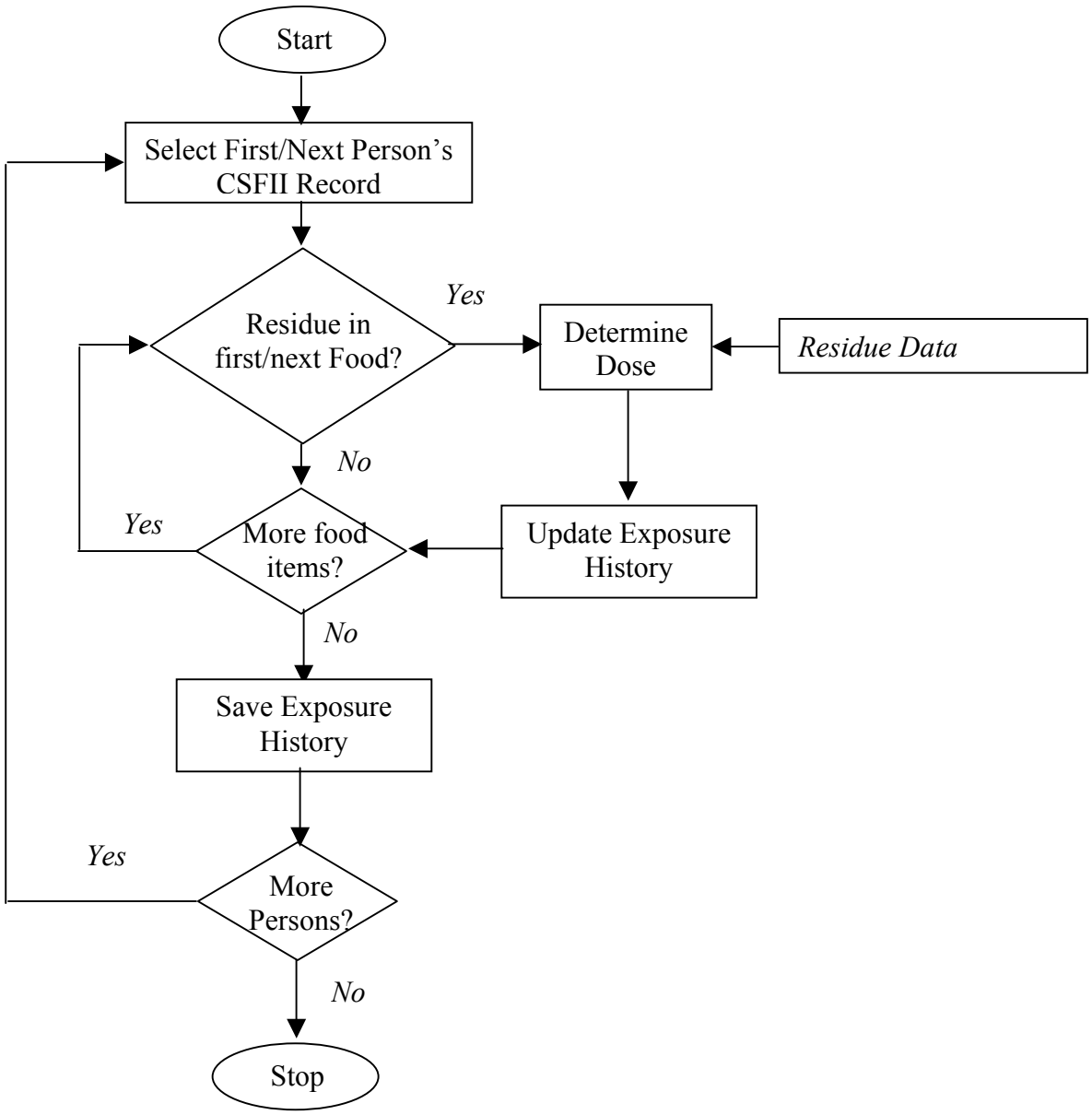
This cycling through the modeled persons is programmed using a second loop called the individual loop. The individual loop is outside of the exposure event loop. This continues until there are no additional persons left to model. The output is a set of route- and source- specific dose for each of the modeled persons. This set of doses characterizes the inter-individual variation in dose across the population for the time step.

Dietary Models as an Example of POMs

Dietary software programs such as DEEM-FCID™, LifeLine™, and CARES™ are examples of POMs, see Figure 6. When modeling a daily dietary dose, all three models pull a dietary record for one person from the USDA Continuing Survey of Food Intakes by Individuals (CSFII). The time step is one day. The CSFII record contains the name and amount of each food item the person consumes on a day. Using this record and a list of foods that have pesticides residues, the models go item by item through a person's daily diet. For each food item, the model checks to see if there was a residue on that food item. If there is no residue, the program goes on to the next food the person consumes. If there is a residue, then the models determine what is the concentration of the residue and what is the dose from consuming the food item. This dose is added to any doses from other food items. At the end of the list, the total dose of pesticide from all foods is determined and given as a model output.

In these models, the information on the co-occurrence of exposure comes from a single survey "record". The record specifies which foods and the amount of those foods are consumed on a given day. This is an example of a "record-based" POM. The model's outputs are a distribution of the oral doses that reflect inter-individual variation in the doses of chemicals that occur in foods in the population.

Figure 6. Models of Inter-individual Variation in Dietary Dose for One Day



Microenvironmental Models as an Example of POMs

Microenvironmental models are air models that track persons through a series of microenvironments, see Figure 7. Air concentrations of contaminants in the microenvironments are modeled or measured and the dose from inhaling the contaminants in each microenvironment is determined. Examples of such models include:

- AirPEX (Air Pollution Exposure Model);
- BEAM (Benzene Exposure Assessment Model);
- HEM (Human Exposure Model);
- pHAP (probabilistic Hazardous Air Pollutant exposure model);
- pNEM (probabilistic NAAQS Exposure Model);
- SHAPE (Simulation of Human Activities and Pollutant Exposure);
- SHEDS (Stochastic Human Exposure and Dose Simulation);
- HAPEM (Hazardous Air Pollutant Exposure Model); and
- SCREAM (South Coast Risk and Exposure Assessment Model).

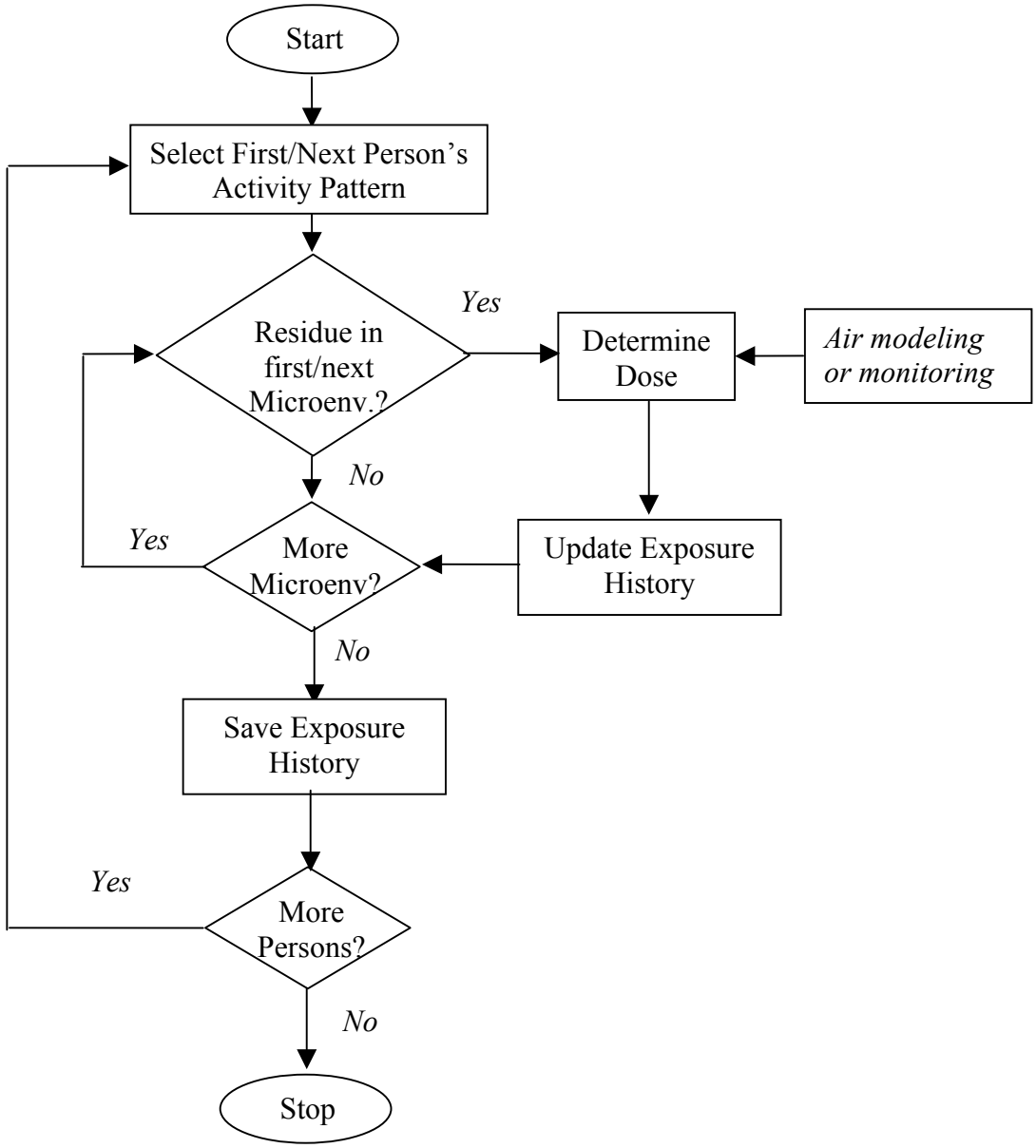
A similar approach also is used in SHEDs for inhalation exposure

The models begin by selecting an activity pattern from a survey of humans activities such as NHAPS, CHADS, or California activity pattern surveys. These records consist of diaries of one person's daily activities. The records specify the microenvironments the person occupied during a day (bedroom, kitchen, car, office, etc) and a description of what activity was performed in that microenvironment. The record also supplies information on the person's age, gender and other characteristics. The models then select the first microenvironment and determines the inhalation dose given the person's breathing rate, duration of time in the microenvironment, and the level of contaminant in the air of the location. In some models, the breathing rate is estimated using the description of the activity and a determination of whether it involves low, moderate or high level of exertion. This determination along with the age, gender, and weight of the person can be used to derive a breathing rate (Layton, 1993).

Once the dose is determined, the model moves to the next microenvironment. This process is repeated until all microenvironments are completed. The total inhalation dose is then determined. In addition, doses from specific microenvironments are saved for the

determination of relative source contribution. This is repeated for each person in the population of interest. Like the dietary models, these models are examples of record-based models.

Figure 7. Microenvironment Models of Inter-individual Variation in Inhalation Dose for One Day



Modeling Multiple Chemicals

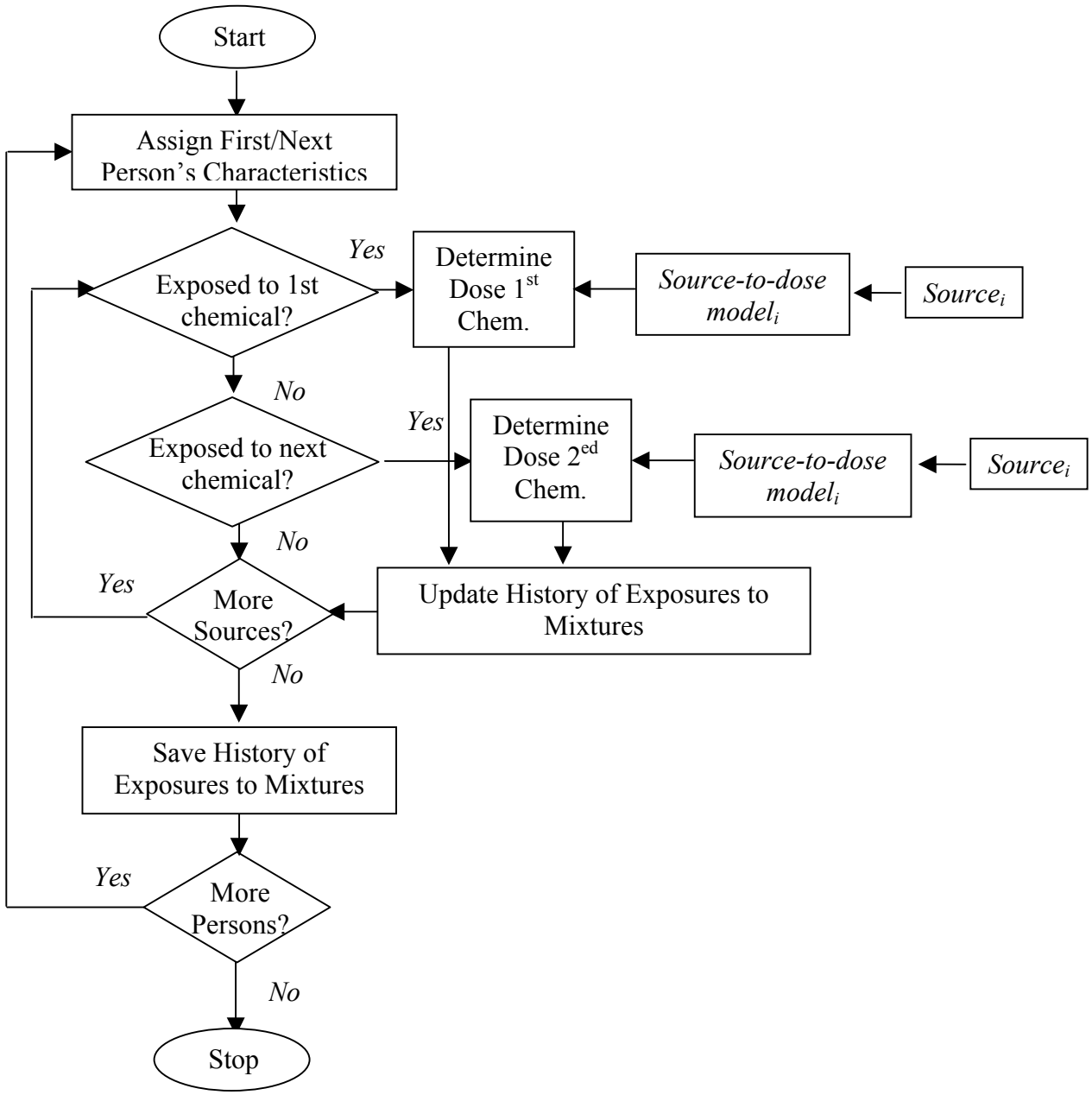
One of the requirements of the Framework is the ability to model exposures to multiple chemicals. The POM approach makes the extension of the model from one chemical to multiple chemicals straightforward. Figure 8 presents a flow chart of a model of the concurrent exposure to two chemicals. While the flow chart presents the process for two chemicals, the process could be applied to any number of chemicals[19].

Like the model of a single chemical, this model begins with assigning the characteristics to the person. In the exposure loop, the model first determines the exposures to sources of one chemical and then the exposures to the subsequent chemical[20]. This process continues until all sources of either chemical have been evaluated. The model then moves on to the next person. The outputs of this process are the route-specific doses for each of the chemicals to the modeled person for the time step. This approach is used in the Calendex™ and LifeLine models™ used by EPA in the recent assessment of cumulative risks from organophosphorus pesticides.

This approach produces estimates of the unique mixture of doses for a time step (such as a day) and each person. This mixture of doses can be used to investigate the total risk to a person from concurrent exposure to multiple chemicals. Having this data on multiple persons provides the basis for measuring inter-individual risk across the population.

[19] At this point, models may also require modeling the temporal changes in the microenvironment in a parallel to the individual. This can be important if there is an interaction between individual chemicals.
[20] The chemical is subsequent only in the sequential architecture of the model. Exposure to one chemical may precede the exposure of the first during the time step.

Figure 8. Person-Based Model of Inter-individual Variation in Exposures to Multiple Chemicals One Time Step



Longitudinal Modeling

In the above examples, the exposures are assumed to happen during a single time step. The time step is sufficiently short that the order or temporal pattern of the doses are not important. For example, in the dietary models, the dose could have occurred in the morning or evening meal. In addition, the exposure characteristics of the person did not change over the day. Finally, the sources were sufficiently well defined that the model inputs could be assumed to be constant during the day (e.g. a single residue occurred in a food item, or a single average air concentration existed in a microenvironment.)

The Framework requires the ability to evaluate exposures that happen over long periods of time (years, decades, or a lifetime). During these periods, none of the above assumptions about constancy will be true. Residues in food and water change from day to day. Air residues change with the source term and with meteorological conditions, sometimes over scales of hours or minutes. Physiological parameters change as a person ages. Activities and diets also change from day to day.

In order to model intra-individual variation, the Framework must have the ability to model how exposure-related characteristics of the persons and the source change with time. This is achieved by explicit modeling of intra-individual variation.

In the Framework, the intra-individual exposures (also referred to as longitudinal exposures) are modeled as a series of time steps. During a time step, one or more events take place. As discussed above, a time step is a period sufficiently short that all of the inputs to the exposure-to-dose models can be viewed as constants. The intra-individual variation is modeled as a series of events or time steps. Figure 9 presents the flow chart for a model of exposures that occur over multiple time steps. (For simplicity, the flow chart addresses a single chemical; however, the approach applies to models of multiple chemicals as well.)

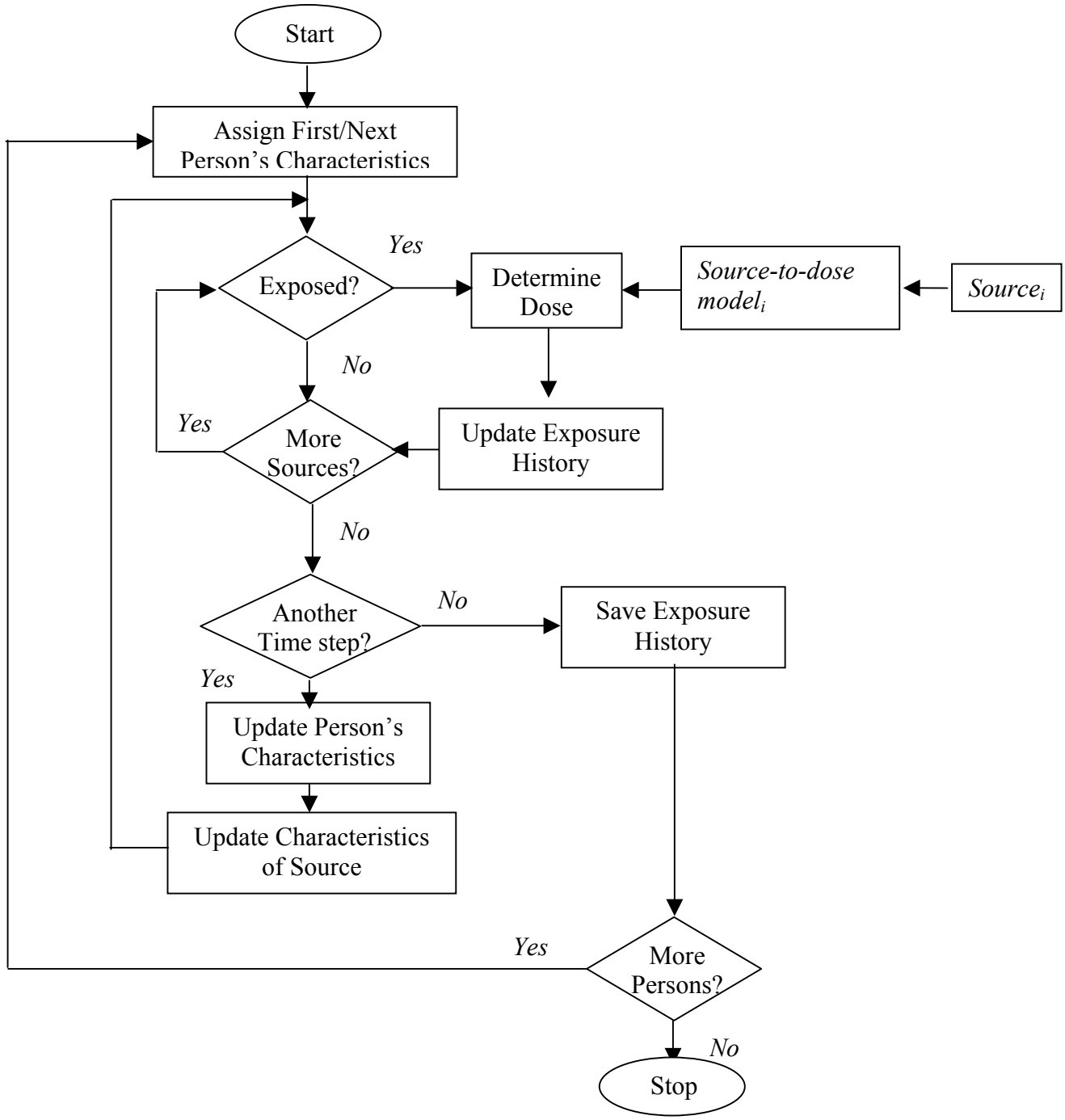
Modeling multiple time steps is achieved with an additional loop called the time step loop. The time step loop occurs between the “exposure event” and the “individual” loops. In this loop, the model performs the exposure event loop, saves the exposure data for that time step and then determines if there is an additional time step to be modeled. If there is an additional step, the model modifies the characteristics of the person and the exposure

sources to reflect changes that occur between the two time periods[21]. Once the characteristics are revised, the model then re-enters the exposure event loop. If there are no additional time steps to be modeled, the model moves to the next person. If there are no additional persons, the model stops.

In general, the Framework would use the characteristics of the person at one time step to predict characteristics at a subsequent time step. For example, body weight would not be expected to significantly change from day to day but would increase over ages 0 to 18 and decline after 50. Exposures can be highly correlated between one day and the next. Painting a room in a home will result in a release of glycol ether on the day that the paint is applied and on subsequent days. A detailed discussion of how the person's characteristics and the characteristics of the source are modeled over time is present later in this chapter.

[21] At this step, the model can include temporal process for the person, the environment and the impact of a person's activity on the environment. For example, a person walking through a room will re-suspend particles and increase air levels to which the person is then exposed.

Figure 9. Person-Based Modeling of Inter-individual Variation in Dose-Multiple Time Steps



The output from this longitudinal model is an "exposure history" for each of the modeled persons. The exposure history consists of the route- and source-specific doses for each chemical for each time step. The exposure histories of the modeled persons reflect both inter- and intra-individual variation. This approach has been used in all of the longitudinal models developed thus far (LifeLine™, CARES™, SHEDS™, APEX, and Calendex™).

This output can be used in a number of ways.

> First, the data can be averaged to give estimates of the average dose over longer periods of time. Thus, if the time step was a single day the model could be run for 365 days and then the daily doses can be averaged to give a prediction of the person's annual average dose.
>
> Second, the highest daily dose can be determined by ranking the 365 daily doses for a person. This "peak" daily dose can be used to evaluate acute risks that the person receives over time.
>
> Third, the history can be randomly sampled to give the exposure that occurs on a random day[22].
>
> Fourth, the exposure histories can be used as inputs to PBPK models. Such models can be used to predict the time course of internal doses that occur because of total exposures. These internal doses can be used to estimate doses to the reproductive organs and the fetus. Because the data are longitudinal exposures for a specific person, the cumulative impact of chemicals, their metabolites, and cellular damage can be modeled. Because exposure histories are available for each person modeled, the inter-individual variation in such measures of cumulative impact can be modeled.

Modeling Uncertainty

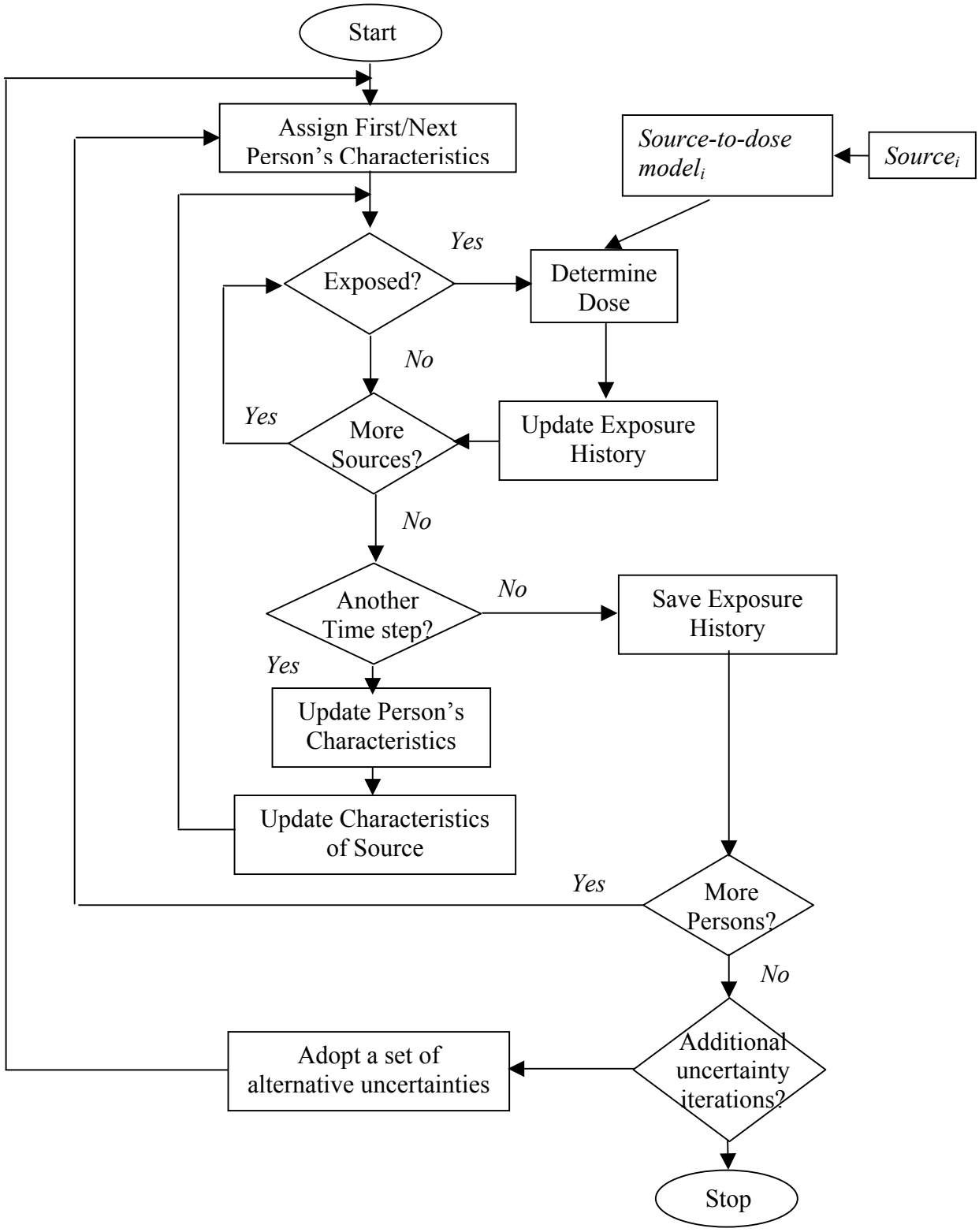
Up to this point, the modeling approach has only modeled variation, specifically, the inter-individual variation in a person's characteristics and the variation in the number and characteristics of the exposure events in individuals' lives. Uncertainties in the inputs and their impact on the resulting dose estimates have not been discussed.

The estimates of exposure produced by this Framework are subject to a number of uncertainties. Inputs to the model are subject to uncertainties from bias, analytical methodologies, or limited sampling size. In addition, use of models results in additional uncertainty (modeling uncertainty) (EPA, 1992). Finally, there are unknown sources of uncertainty (surprise; Hammit and Shlyakhter, 1999).

22

Modeling of uncertainty cannot be performed for all sources of uncertainty. However, uncertainty in inputs and in algorithms can be characterized using a fourth loop and outermost loop called the uncertainty loop. Figure 10 presents the flow chart of a model that addresses multiple sources, inter- and intra- individual variability and uncertainty. The model begins with the longitudinal model described in the prior section and adds an outer loop for uncertainty. In this outer loop, the model adopts alternative analyses of exposure that reflect uncertainty in model inputs and model algorithms. For example, if the distribution of air concentrations in homes is described by a lognormal distribution with an uncertain mean, alternative values for the mean can be modified in the outer loop.

Figure 10. Person-Based Modeling of Uncertainty and Inter-and Intra-individual Variation in Dose-Multiple Time Steps



The approach of nested loop has a long history in use of modeling uncertainty and variability (Bogen and Spear, 1987; Hoffman and Hammonds, 1994; Price et al. 1996). The approach is also used in SHEDs (EPA, 2002)[23].

The output of this joint model of uncertainty and variation is an uncertainty distribution around each of the outputs of the model described in the previous section. Thus while the prior model can provide an estimate of the 95th percentile for an annual average exposure to individuals in a population, the additional loop allows the determination of confidence limits on that estimate.

The Comprehensive Chemical Exposure Framework

The project team believes that the modeling approach described in Figure 10 provides a conceptual basis for the Framework. The approach, while simple, has the ability to model doses from acute to lifetime doses, for ages varying from conception through birth to any age. The approach can be extended to any number of chemicals, sources of exposure, and routes of exposure. The approach allows for the correct separation inter- and intra-individual variation and uncertainty. Finally, the proposed approach is consistent with the majority of models currently under development by EPA, academia, and industry.

Building the Framework using person oriented rather than source-to-dose modeling design provides a number of advantages. First, it is the risks to individuals and how they change as a function of sources and mitigation that is the ultimate goal of the model. Second, inter- and intra-individual variation in dose and risk are key outputs for the model. Thus, the model should begin with a specific focus on inter- and intra-individual variation.

Third, defining internally consistent doses from exposure to multiple sources and routes of exposure to one chemical or to multiple chemicals can only occur if the same individual is modeled for each source. Focusing the modeling on the person allows for the calculation of internally consistent models of the person's exposures with regard to time, location, age, and source. Fourth, focusing on the person allows the model to track each person over time (from the characteristics of the parents at conception, the characteristics of the mother during pregnancy, and the characteristics of the individual from birth to the end of his or her life). This allows the calculation of doses for any duration from one day to a lifetime. Finally, these models allow the linkage of doses to the concurrent physical characteristics of the individual (age, sex, gravidity, health status, etc.) that may be relevant to the prediction of risk.

Computer programs based on this looping structure has the additional benefit of increasing linearly with the number of sources. This is in contrast to programs such as

[23] An alternative model structure would be to place the uncertainty looped as the inner most loop. Such a structure has the advantage of limiting the uncertainty to specific sources but may increase the complexity of data management.

decision tree analysis where model complexity and run times increases geometrically. This means that large numbers of sources can be tracked in one model. In addition, adding an additional source to an existing model can be easily performed.

While having established the fundamental architecture of the model, there are a number issues in the design of a practical Framework. These issues are discussed in the next section of this chapter.

Linking to PBPK Models

The Framework provides an ideal basis for the integration of exposure models with PBPK models. PBPK models require longitudinal information on route specific doses and data on the nature of the individual. The Framework's focus on the individual provides all of these data.

The Framework begins with the definition of the exposed individual. This definition provides the basis for assigning consistent values for all of the physiological parameters relevant for PBPK modeling. In the CARES™ and LifeLine™ and SHEDs models the individuals have factors such as age, gender, and body weight defined. As shown by Price et al. 2003 it is possible to define all of the relevant physiological characteristics (organ volumes and organ specific blood flows). PBPK modeling is by definition longitudinal. That is the model; the change in internal doses over time as a function of exposure and metabolism. The longitudinal aspect of the Framework can provide this temporal dimension. The exposures are also route specific and longitudinal in nature. Finally, PBPK models require metabolic information (breathing rates and cardiac output) that is dependent on the individual's activities. The Framework provides this information because the activities of the individual are modeled[24].

Technical Issues in the Construction of the Framework

This section of the project discusses three technical issues in the development of the Framework. These issues are defining the population, managing correlations between inputs, and managing the vast amounts of data produced by the Framework. These discussions are also intended to assist in the identification of data gaps and areas of future research needed for comprehensive exposure assessments.

Modeling Inter-individual Variation of Exposure-Related Characteristics in Populations

The goal in modeling of inter-individual variation is to assign sets of value that simulate the sets of values occurring in the population of interest. This requires that the model achieve two criteria; first, capture the range and distribution of values for each of the

[24] The METS data for the CHADS database is an excellent example of such data.

exposure related characteristics of the persons in the population of interest, and second capture the correlations between the values of the characteristics in the persons. In order to achieve these goals the model must first define the population being simulated.

Defining the Population

Exposure assessments performed under the Framework must begin with a clear definition of the modeled population. Without a clear description of the population being modeled, it is possible to bias the assessment and misuse data. Populations can be defined in three ways: in terms of the specific sources of exposure included in the assessment, the availability of data, or the use of independent demographics.

The population that is modeled in source-to-dose models is typically the population receiving a dose from the source. Examples of this approach include consumers who use a product or persons living downwind or downstream of a point source. This approach raises some difficulty in that such specific populations may differ from the general population and, thus, data on variation taken in the general population may not be relevant.

Defining the population in terms of exposure becomes unwieldy when multiple sources of exposure are being modeled. Consider an assessment that evaluates two phthalates using the sources to identify the population to be modeled (Scenario 2 in Chapter 3). One phthalate is used in cosmetics and the second in children's toys and furniture. Each phthalate has a distinct exposed population (toys - small children and cosmetics- older children) but have some potential for overlap (small children passively come into contact with makeup on adults and some young children actively use makeup). Considering a third source of exposure to the phthalates, food packaging, creates a third exposed population that overlaps the first two. Such cumulative populations become difficult to describe or to model.

The alternative approach is to define the population in terms of specific demographics. Examples might include, the general U.S. population, all persons living in town houses, workers in a specific SIC code, or all children aged three. Under this approach, persons in the population are included in the model whether or not they are actually exposed to one or more sources and the model determines if they are exposed or not exposed. If they are not exposed the model predicts a dose of zero for the persons. The result is a prediction of the distribution of doses in a population that includes some fraction of the population having zero doses.

This approach has a number of advantages. First, it allows the use of national or local demographic data for the population. Second, the model can be extended to new sources of exposure. The drawback to this approach is that it wastes the computer's time in selecting and evaluating non-exposed persons. However, this drawback can be minimized by tailoring the model to the demographic groups with the greatest potential for exposures. For example, if the exposure is associated with swimming in a home pool, the model can be limited to homeowners with pools.

A variation in this approach that has been used in certain programs is to sample for a predefined population. CARES™ has created a "reference population" of 100,000 individuals who have detailed information on their properties specified. The population is designed to be representative of the U.S. population (Sielkin and Holden, 2001). In Calendex™ all adults are based on the persons who participated in the 1994-96, 98 Continuing Survey of Food Intake by Individuals.

A second variation is the Population Based Modeling used by GIS based models such as APEX and MENTOR. These models use census data to define the composition of populations in specific locations. These data are then used to assign characteristics across the simulated population (Georgopoulos et al., 2002).

Once a population has been defined for a model, the distributions for exposure related characteristics can be identified and developed. These characteristics include parameters required to characterize:

- The probability of exposure;
- The intensity of exposure; and
- The magnitude of the risk.

Characteristics that predict the potential for exposure may include age, gender, income, housing, and geographical location. Characteristics that affect the intensity of the exposure and the resulting dose would include weight, breathing rate, and behaviors such as the frequency and duration of hand-to-mouth events. Characteristics that influence the health risks would include general health, age, gravidity, and gender.

Modeling Correlation and Autocorrelation

A major concern in defining the characteristics is the correlation among values that occur for different factors. Failure to capture correlations can affect the estimates of the distributions of dose and risk. There are two approaches to defining correlations. The first approach is to rely on data taken from a single person. This is referred to as a record-based approach. Record-based approaches capture the correlations between the values of a person's exposure factors empirically, since the data come from a single person. As shown in figures 6 and 7, record-based approaches have been used for the evaluation of dietary and human activity pattern based assessments.

There are, however, drawbacks in relying entirely on a record-based approach. First, while surveys have been performed of human activities and diet, no survey has been performed that captures all of the behaviors that are associated with chemical exposure (use of consumer products, hobbies, home heating system, room sizes, or air exchanges rates). In addition, it is difficult to obtain survey results on a person's behaviors for periods of time longer than one or two days. Therefore, strict reliance on record-based approaches cannot be used to investigate exposures that occur over longer periods of time than a few days. The approach proposed for the Framework (Figure 10) requires the

modeling of exposure-related characteristics over time. Therefore, the Framework cannot rely exclusively on a record-based approach.

The alternative approach is to construct the persons' exposure-related characteristics based on multiple sources of data. This approach; however, must develop method of avoiding assigning inappropriate values to a person.

Longitudinal data generally are not available for exposure-related characteristics. This means that the Framework must also include an approach for modeling autocorrelation in persons. Behaviors are likely to autocorrelated to some degree. If I drive a car to work on one workday, I am likely to drive the car on the next workday. If I like fish, I am more likely to have multiple fish meals over a year then if I do not like fish. If I own a swimming pool, I am more likely to regularly swim than if I do not own a pool. Negative correlations in characteristics of persons and sources occur as well. If I paint a room today, I am not likely to repaint the room tomorrow. Finally, variations do occur despite correlation; I am unlikely to consume fish at every meal in a week, even if I like fish a lot and am a high-percentile consumer.

One of the few sources of such data that are available is the NHEXAS Maryland dataset (MacIntosh et al., 2001). This data set includes data on diet and activity for approximately 80 individuals for 6-8 one-week periods that occurred over an 18-month period. Analyses of this data set have confirmed that such autocorrelations do occur for both activities and diet.

Strategy for Addressing Correlation and Autocorrelation

One approach that addresses this problem is to constrain the range of likely values for a person using a hierarchical system for assigning values to each of the person's characteristics. The goal of this hierarchy is to construct models that initially set values for those characteristics that can be assigned with confidence and use those values to constrain the range of possible values for the remaining characteristics.

The approach begins by classifying the exposure characteristics of the persons into different categories depending on how they vary with time. The categories are fixed, and variable. Variable characteristics are further subdivided into long-term trends, episodic, cyclic, and ephemeral.

Inputs with Fixed Values

A person has certain characteristics that are constant over her or his lifetime. These include sex, race, ethnicity, birth date, body type, and certain other physiological characteristics. These inputs are assigned at the first time step of the model using data on the distribution of the values in the population of interest (e.g., total U.S. population, blacks, low-income, etc.). The major source of data on these fixed properties is the nation's birth records and the records of persons collected as part of the U.S. census.

These records provide the characteristics of the person's sex, race, ethnicity, and place of birth and mother's residence (not only region but also urbanization). This approach would also take advantage of data in the records for characteristics that are not fixed (housing and location) since these data are correlated with the fixed characteristics of the person.

Long-Term Progressions

This class of characteristics includes most of a person's physiological characteristics. Such characteristics vary in predictable patterns. Height increases regularly until adulthood, and remains constant or slightly declines thereafter. Weights similarly increase with height until adulthood[25]. All of these inputs are influenced by and are thus contingent on the fixed properties (sex, race, and ethnicity). Therefore, the selections of the values are correlated with the characteristics already assigned to the person.

In general, data on these characteristics are taken from the findings of the NHANES III surveys. These surveys are, unfortunately, snapshots of data on persons at specific times. Thus, while models of the progression over time can be constructed from these survey data, doing so necessarily ignores the role played by historical changes that would affect the data (e.g., improving nutrition over a period of decades) in an actual population.

Inputs to the models for exposure sources can also follow long-term progression. Such inputs include levels of residues in tapwater (moving plume), decline of POPs in fish, or air concentration following a paint application. The user enters information on the levels and temporal trends of these residues.

Episodic Changes (Non-Periodic State Changes)

Many characteristics change in an episodic fashion; that is, they remain relatively constant for lengthy periods of time, change radically, and then remain constant an additional period of time. These characteristics tend to be associated with major life changes such as entering school, changing jobs, changing residences, marriage, and the birth of children. Characteristics that fall in this category include residence-related inputs (room sizes, yard, or the presence of a pool or garden), occupational-related inputs, and inputs related to exposures in institutional settings (e.g., school, college, or armed services), and child- and pet- related adult exposures.

Episodic changes are modeled in a different fashion than other inputs. In general, at the end of each day (or some other suitable period), the model uses a simple binomial decision on whether these inputs change or not. If the inputs do change (the person moves, takes up a new job, enters school, or begins school) then new values are adopted. The approach makes use of age-specific probabilities of episodic changes that are available from the U.S. Census and the Bureau of Labor Statistics.

[25] In the case of weight, there is a secular change in weight over the last 30 years that should also be considered.

An example of such modeling is the modeling of factors related to residences. Data on residential mobility are available from the Current Population Survey and American Housing Survey maintained by the U.S. Census. These data can be used to determine the probability that a person of a certain age, gender, and SES, living in a specific setting (urban or rural), region, and housing type (single or multiple family residence), will stay in the same location, move to a comparable dwelling unit, or move to a different region, setting, and housing type.

Cyclic Changes

Many characteristics are determined or are influenced by the season and day of the week. These inputs include activity patterns (weekend versus weekday), diet, consumer product use, and air exchange rates. Prediction of values for these characteristics requires any model to track the day and season of each time step.

Ephemeral Changes

Ephemeral characteristics vary from day to day. They describe individual events that may occur more than one time, but unlike the cyclical characteristics without a strong periodicity. Some examples include:

- Was a hard surface cleaner used in the kitchen of this house?
- How much time did the person spend in each area (*e.g.*, each room, as well as lawn/garden)?
- What activity was performed in each room?
- What did the person eat that day?
- Did the person use the chemical in his or her workplace?
- What were the levels of the chemical in each food item consumed on a given day?

These inputs may be purely random. For example, the chemical concentration in a food item on a food item purchased from a store can be modeled as a random sample from the appropriate residue distribution. These factors are relatively simple to model.

However, strong correlations can exist in these characteristics. If I eat large amounts of one food, I probably do not consume large amounts of a second. If I spent eight hours at my job, I am not likely to spend 12 hours doing yard work on the same day

Other ephemeral inputs have aspects that are a mixture of random and cyclical or episodic behaviors. These inputs are modeled as constrained random models. For example, a pesticide used in a residence may be random in the sense that the pesticide is equally likely to be used on a Tuesday or a Wednesday. The probability of the use, however, is influenced by a large number of inputs such as the season of the year, region of the country, type of home, frequency of use, and time since last use. Another type of mixed random-cyclical of particular interest here: maybe I always clean my house Friday afternoon. I may not use a specific cleaner, but if I do use it, then the time of use will always be on Friday afternoon.

Rules for Assigning Values to Characteristics

Once the inputs are categorized, the following rules are used to evaluate the temporal changes in input values in a simulation of a person's life.

1. A person's fixed characteristics are always assigned first. This allows the fixed characteristics to be used in the consistent selection of subsequent variables. Values selected should be internally consistent.

2. Once a person has been assigned permanent characteristics, a person's time-varying inputs are assigned for each time step of the person's life. The assignment of the values on any time step is contingent on the values assigned to prior time step. Thus, the model begins with exposure during the earliest times step and moves forward in time. For example, the characteristics of the person's first home can be based on the region and setting (urban or rural) of their (or their mother's) home, as well as their (or maternal) socioeconomic status (SES).

3. Each day of a person's life is defined in terms of season and whether it is a weekend or weekday. This allows the model to take advantage of the relative consistency between work (or school) days and weekends. In addition, many source of chemical exposures are seasonal (exposure related to heating systems, outdoor products, etc.)

4. Temporal changes in episodic variables are modeled by a series of binomial decisions (the variable either changes or remains the same). The decision is made on a daily basis (or at some other appropriate frequency). The probability of change and the selection of new values can be determined from studies of populations that are consistent with the person's age and other characteristics previously assigned. Once a change has been made (change in residence, etc.), all affected variables, but only affected variables, are modified. These binomial models are in some ways similar to branching models but are more flexible and have the advantage of not requiring the user to exhaustively define all possible outcomes.

5. Selection of ephemeral inputs is based on a random or constrained random models. These models make take several forms. One method is to randomly sample from records that are constrained to be consistent with relevant inputs such as the day of the week, season, age of the person, gender, residence type, and region. This approach has been used for selecting activity patterns and dietary records. A second method is to use a binomial model where the probability of an input changing is contingent on relevant inputs such as season, region, prior use, and residence.

6. The temporal patterns of change for characteristics are determined independently. Changes in values are never automatically linked, unless there is a sound reason for predicting a correlation. For example, moving to a new home does not change a person's height but does change the room sizes.

This approach rules address inter- and intra-input correlations in a number of ways. First, records of behaviors (diets and activities) are used wherever possible. Second, contingent modeling is used. Under this approach, data are organized into a series of contingency tables that are used to guide the selection of input values.

An example of this approach is the selection of height, weight, and surface area in LifeLine. Height is tracked across a person's life. At each age, a person's height is determined based on the person's height at an earlier age and the person's sex, race, ethnicity, and age. Given this new height, a new weight is selected. Once the height and weight are selected, the total surface area and the surface area for the hands and other body parts are selected. In this way, the body weight and surface areas of a person are kept internally consistent with across a person's entire life.

In a similar fashion, the selection of records from separate studies can be made contingent on the values of inputs already assigned to the person. For example, the selection of an activity pattern can be linked to the person's age, season, type of home, and presence of a yard. In this way, the data used for the characteristics of the residence and the person's activities are consistent.

Correlation between inputs is also dealt with by modeling temporal trends for each of the inputs separately. For example, room sizes will remain constant until a person moves, while air concentrations will change from day-to-day based on use of consumer products, season, and air exchange rates.

Temporal correlations in source terms are managed by directly modeling the day-to-day changes in sources. For example, if a room is painted on one day, the following day's exposure is explicitly linked to the prior day's usage. Levels in air and on surfaces will be calculated in terms of the levels that occurred on the prior day.

Modeling Longitudinal Patterns

An example of how the consideration of different types of data can be used in modeling can be seen in MacIntosh et al. (2003). In this study, longitudinal exposure information collected as part of the NHEXAS-MD study is used to fit and evaluate models of longitudinal activity patterns derived from short-term measures. The endpoint studied was the total time spent in a home in one day. Models of the distribution of seven day and annual average of the endpoint were calculated by sampling individual records and constructing synthetic longitudinal patterns. The predictions of the seven day and annual average values of the endpoint were improved by stratifying the sampling based on fixed characteristics of the individuals (employment status) and further improved when sampling took into consideration day of the week (cyclical).

Modeling the Person, Family Structure, and Residence

The characteristics of the person go beyond the activities and physiology. The person's potential for exposure will require defining the person's residence and family structure. The reason for this is that the potential for exposure will be affected by both the characteristics of the residence and the activities of other persons in the home.
The characteristics of a home have a great influence on the potential exposure. Factors that should be considered in the model included room sizes and air exchange rates, the relationships between room locations, heating systems, and the presence of attached garages, workrooms, and home offices. These factors must be defined in order to keep the source-to-dose models consistent.

The family structure has a great influence on exposures. An adult with infants in the home has different activity patterns, diets, and uses different products then adults without children. Thus, the model must assign a family structure to the person (other adults, children, infants, etc) present in the home.

Modeling family interactions is an open-ended task that may never be amenable to computer programming. Therefore it is critical that the user define the sources that will be modeled and limit the modeling of other family members to those events that affect the person's exposures to those sources. For example, in Scenario 1, EGBE exposure can occur from the use of hard surface cleaners. The application of EGBE in the kitchen by one member will create EGBE level in the indoor air of the entire house and exposing all family members including the modeled person. Thus, use events of EGBE by any household member will need to be modeled. However, the other activities of the other family members not relevant to the person's EGBE exposure do not need to be included in the model.

Management of Outputs

One draw back to the proposed Framework is the amount of data the model generates. Consider the following scenario. An analysis of inter- and intra-individual variation is performed and generates estimates for 1,000 children. The model determines inter- and intra-individual variation of daily dose over the two-year period from the children's second to fourth birthdays. This requires modeling 730 days (2*365 days). If the exposures occur by three routes, then for each day there are three doses, dermal, inhalation, and oral. The total number of doses modeled is:

= 1,000 * 730 days * 3
= 2,190,000

If the uncertainty in the estimates is evaluated then an additional 500 iterations of the uncertainty loop are performed.

= 2,190,000 *500
= $1.9\ 10^9$

As this demonstrates even a modest number of iterations for uncertainty and variation can result in very large data outputs. These outputs result in large files and long run times.

One approach that can assist in this problem is to decide prior to the assessment which outputs are of interest and save only those outputs that are of interest. For example, if the analysis of interest is annual exposures then the model can be instructed to average the 730 days into two annual doses. This would reduce the output files 365 fold. If confidence limits are needed on the mean and the 95th percentile of the variation in the population, then the mean and the 95th percentile of the simulated population can be determined as part of the uncertainty loop and saved. This will reduce the output to 1,000 outputs (500 estimates of the mean and 500 estimates of the 95th percentile). The drawback to this approach is that the model will have to be rerun if alternative measures are required.

Design of Software for Implementing Framework

The request for proposals, while making it clear that no code would be developed, requested the development of a modular architecture for a computer program that would implement the Framework. The software should be modular, open, and probabilistic.

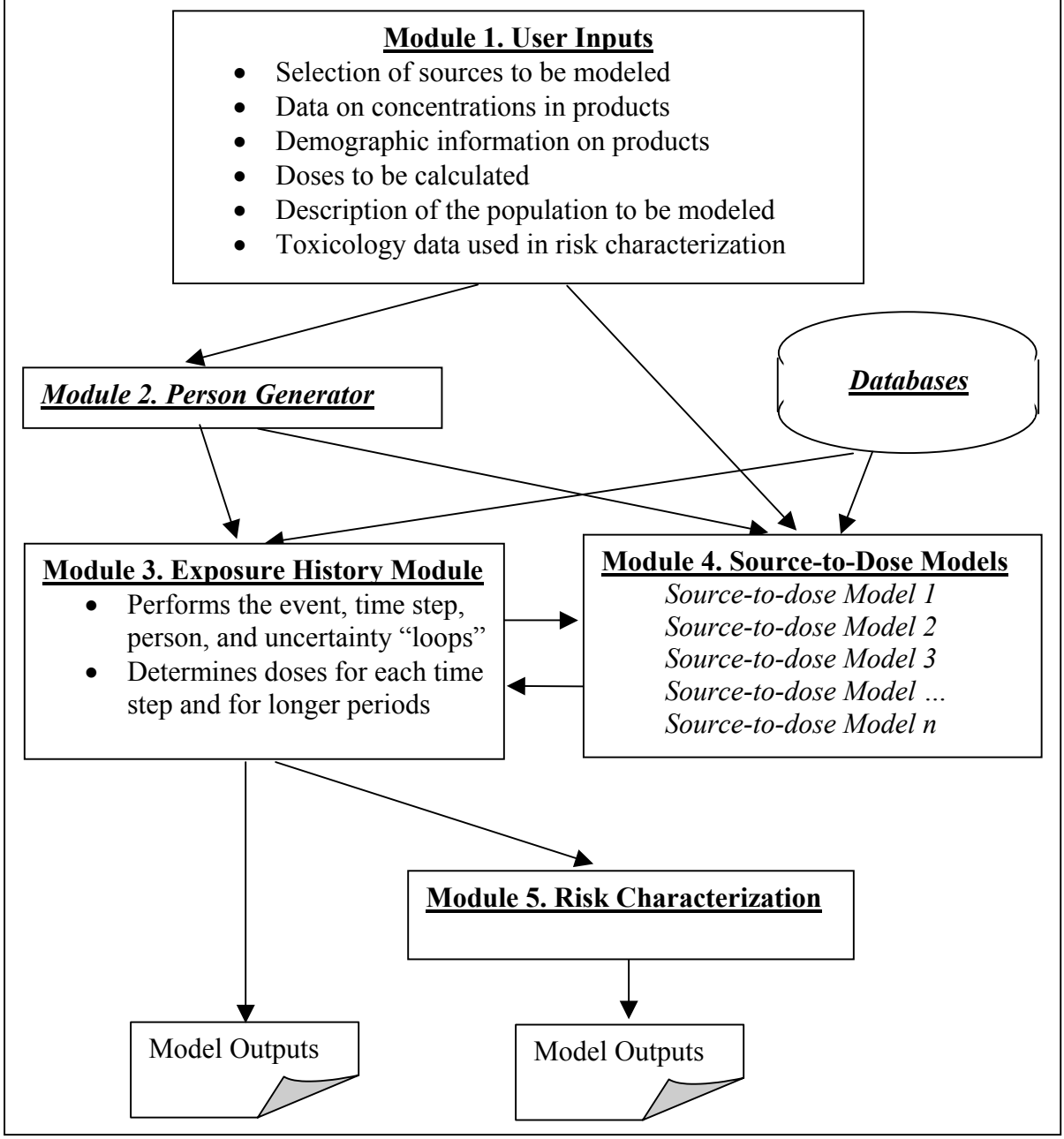
A person-oriented software design that could be used would consist of six modules (or classes of modules):

1. User inputs/preferences module;
2. Person/population module;
3. Exposure history module;
4. Source-to-dose modules;
5. Risk characterization modules; and
6. Output modules.

The model would also include a number of databases of demographics[26] data. Figure 11 presents the relationships among the first six modules. The arrows indicate the flow of data.

[26] Source demographics are the data that describes the patterns of use of products containing the compounds of interest. These data include information on frequency of use and the factors (season, age, house type, occupation) that will influence the frequency of use.

Figure 11. Modular Design for Software That Implements the Comprehensive Chemical Exposure Framework



User Inputs/Preference Module

In this module, the user specifies the sources to be modeled, population to be simulated, and the dose and risk estimates that will be determined. The user also indicates what data will be saved and made available for either documentation of the analysis or for subsequent analyses.

Finally, the user also enters the analysis specific data. These data are data required for the analysis that is not available from the model's databases. Examples of such data would include the mass of chemical released by the modeled product, air monitoring data, and chemical-specific properties. If risk characterization were required, then the data would include the toxicity data for the compound(s) being analyzed.

Person/Population Module

This module generates the characteristics of the "modeled people". The model of a person consists of a series of "vectors" of values for the characteristics that describe a person on a time step. Separate vectors are defined for each time step of the model. As discussed above the characteristics fall into three categories, those that define the potential of exposure, those that define the magnitude of the doses received from a source, and those that define the risk from the exposure. The properties that would be included in this vector include but are not limited to:

- Gender, age, and ethnicity (note that gender and ethnicity remain unchanged);
- Body weight, surface area, and surface area of specific portion of the body;
- Daily activities and daily diet;
- Health status, gravidity, and nursing status; and
- Characteristics of the person's residence, primary activity (e.g., occupation, school), and geographic location.

This module will also provide the characteristics for the prenatal exposures. These characteristics would include the characteristics of the fetus (gestational age and weight) and the mother.

Each simulated person differs from the prior person (has a different set of vectors). The person/population module varies the values in each person's vectors to mimic the population of interest (the entire U.S. population, persons living in one-story townhouses in Massachusetts, adults working in a manufacturing plant using a solvent, etc.).

The data generated in the person/population module are used in a number ways. First, the module defines the values of parameters (surface area, body weight, etc.) that are used in the source-to-dose modules to predict the dose received by each route on each day of the person's life. Second, the characteristics of the person, their residence, job, location (census region), and setting (urban and rural) are inputs to the models of the probability of exposure to specific sources. For example, if a person is in a residence with no yard then there is no potential for use of a chemical fertilizer. Third, the module provides the

length of the person's life and other factors that form the basis for construction of the person exposure and dose histories. Finally, the module provides the data for determining risks, if age, gender, or other factors are believed to be relevant to the estimate of risk.

This module would contain the code that selects data from the model's databases and tells the model how to select values for the person being modeled and when to select different values as the person changes over time. This is the portion of the model that would manage the issues of correlation and autocorrelation.

The person module also defines the microenvironments (locations) where the exposures can occur in a given time step. These locations must be defined in a consistent way across all modules of the model.

There is a tradeoff in the number of types of microenvironments that are modeled. It is desirable to have a model that tracks persons through all types of rooms and environments (buses, trains, planes), and institutions (schools, daycare, military service, retirement/nursing homes). However, data on the frequency that a person visits a specific microenvironment, the duration of time spent there, and the activities that are performed often limit the number of environments that can be modeled. This will be a commonly encountered data gap.

The nature of the sources of the chemicals being modeled will also affect the number of microenvironments that require modeling. As a result, the model will require the ability to expand or reduce the number of microenvironments that are modeled. This is done by including as large a number microenvironments in the person/population module as possible and simply turning off the unneeded locations.

Finally, the detail with which microenvironments are modeled (e.g., as a whole versus individual rooms) will have a great bearing on the complexity of the model and associated run times.

Exposure History Module

The second module is the heart of the program. This module contains the four nested loops described in Figure 10:

- The exposure event loop where each chemical's sources are evaluated on each time step and the route and source specific doses are determined;
- The time step loop where a person is moved through time, modifying his or her characteristics and the characteristics of the sources;
- The person loop where the models moves from one person to the next; and
- The uncertainty loop where alternative modeling assumption are selected and used to model inter- and intra-individual variation.

This module draws on the person module for data on each persons characteristics for each time step. Using this data, the modules determine whether the modeled person is exposed to a specific source. To do this the code in the module must use data on the probability or

frequency of exposures to specific sources and determine how the characteristics of the person influence the frequencies of exposure. This portion of the model attempts to answer the question:

> *"What is the probability that on a given day in a given location a person with specified characteristics (defined by the person/population module) will have an exposure to a specific source that has specific characteristics (of a certain duration and intensity)?"*

This portion of the model is dependent on surveys of product usage, data on the temporal and spatial variation in environmental sources, and industrial hygiene data. The module also includes rule-based approaches. Two examples of such a rules are:

1. If a specific spray cleaner is used once by a person, then the same cleaner is likely to be used the next time (one bottle provides multiple applications), and
2. If a window is cleaned with a product on one day, then the probability of cleaning the window with the same product on the following day is reduced.

This portion of the model is where data gaps are most likely to occur. The gaps will include missing data on the frequency and characteristics of exposure events and how they are correlated both with demographic information and over time.

This module will contain sub-modules for each source of exposure to a chemical(s) of interest. Sub-modules would be developed for sources such as:

1. Paints
2. Cleaners
3. Toys
4. Furniture/furnishings
5. Occupational exposures
6. Exposure to petroleum hydrocarbons during transportation
7. Building products and coatings
8. Distant sources
9. Diet (General)
10. Diet (Local foods such as self caught fish, backyard gardens, "pick your own", etc.)
11. Tapwater

These sub-modules will be called up if the model determines that an exposure to these sources occurs in a specific time step. The sub modules would then call on the source-to-dose models in the source-to-dose module to determine the dose for each source on each time step.

Finally, the exposures and doses from each event are summed by source or route to provide a series of doses for the time step. This module also converts these doses into average doses that occur over longer periods of time. This is performed by determining the running average for different periods in the person's life. For example, if the time step is one day and the user is interested in seven-day-average exposures then this module will track the doses on days 1-7, 2-8, 3-9, etc. The result is a dose history of the person that

includes the dose that occurs on a specific day and the average dose that occurs on that day and the six prior days.

The outputs of the module are the exposure histories for the simulated persons. These histories can include the route specific and total doses for each or all sources. If the user requests average doses for long periods of time (average over n days) then the history will include both the dose that occurs on a specific day and the average dose that occurs on the "n" prior days.

Source-To-Dose Modules

The third type of module is the source-to-dose models. There is one of these models for each type of source. This portion of the model answers the question:

> *"What is the dose (or dose rate) that a person receives from an exposure event given the person's characteristics (Module 1), the nature of the exposure event (Module 2), and time and location where it occurs (Module 2)?"*

In this module, separate algorithms are used to estimate doses that a person receives as the result of an exposure event and the key parameters for those equations (air concentrations, dislodgeable concentrations on surfaces). Such models would include indoor air models, models of dislodgeable residues, and other mass-balance models of fate and transport. These estimation algorithms take advantage of the data on the person, his or her residence, and the season and geographic location that have been defined by the other modules. For example, an event during the winter in a new residence in the Northeast might have a lower air exchange rate than in other regions under similar weather conditions, due to the generally "tighter" housing stock in that region.

The models should include dose estimates for multi-route exposures for a single source. In the case of tapwater dermal, inhalation, and oral exposures would be determined. In the case of residue on surfaces, the module would track both dermal and oral (hand-to-mouth) exposures.

These modules also represent an aspect of the overall model where data gaps are likely to occur. Such gaps would include missing or poorly defined models of exposure, fate and transport.

Risk Characterization Module

The final module in the Framework uses the data on the person and the exposure histories to construct risk histories of the person. The risk models currently used to evaluate the hazards of chemicals (incremental cancer risk, Hazard Index, Hazard Quotient, Margin of Exposure, Percent Reference Dose) can be calculated in this module. However, this Framework allows the module to contain more complex dose response models. For example, the risk posed by a chemical may require that the dose exceed some threshold

for a fixed period. The proposed approach for this module would allow the determination of the number of persons who have such patterns of sustained doses, the number of times such patterns occur, and under what conditions the patterns occur.

Demographics Databases

The model would also contain a large number of databases. These databases would include data on factors such as:

- Physiology;
- Exposure related behaviors;
- Diet;
- Activity patterns;
- Product use information;
- Housing information; and
- Hobbies/recreational behavior.

These data would be used by the various modules.

Chapter 4. Demonstration of the Framework using Four Scenarios of Multi-chemical, Multi-source, Longitudinal Exposures

Chapter 2 presents the basic design of the Framework. This Chapter presents a description of the application of the Framework to four scenarios developed by ACC as part of the original request for proposals. A description of the scenarios is given in Appendix A of this report.

All of the scenarios involve residential, transportation-related, or occupational exposures to chemicals. The doses of interest for each of the scenarios are not clearly defined but the Framework is intended to provide doses for any specified averaging time and to address the need for data on inter- and intra-individual variation. In order to demonstrate capability of the proposed approach this Chapter will include modeling of acute, subchronic, and chronic doses. The specific doses will be modeled are:

- One day (acute);
- 30 day (subchronic); and
- The average dose over the age period specified for each scenario (chronic).

Because the proposed approach for the Framework has the ability to model each day separately over multiple years, there will be hundreds or thousands of daily doses for each simulated person. (The variation in each person's doses is the measure of intra-individual variation.) In these scenarios, the model will report the highest of the daily doses on a mg/kg/day basis as a measure of the acute dose. The highest 30-day average on any continuous set of 30 days will be determined for the subchronic dose. The chronic dose will be determined for the entire period specified in each of the four scenarios. Additional doses will be modeled as needed. It should be noted that the approach is not limited to these durations and other doses could be calculated.

The Framework is a Framework that allows the assessment of populations. Thus, it is unclear how the specific scenarios in Appendix A should be evaluated. While the scenarios are not unrealistic, they represent a relatively rare set of circumstances that would not represent the total exposures to the chemicals or the full range of exposures that would be expected in the general population or in the specified age groups.

The approach used in this Chapter is to use the scenario descriptions provided by ACC to select the chemicals, the age ranges, and a minimum set of sources for the analysis. The scenarios will then add additional sources of the chemicals identified in a brief review of the literature to complete the exposure for the chemical. In the example, the exposure event loop will specifically discuss the sources specified by ACC.

The exposure assessment for each of the scenarios will be developed using the following steps:

Step 1. Determine what are the chemicals and sources to be considered;

Step 2. Determine what population will be modeled and the duration of the averaging periods for the doses of interest (acute, intermediate, or chronic);
Step 3. Determine the source-to-dose models required for each of the sources and routes of exposure and the model inputs that are required by each of the source-to-dose models;
Step 4. Identify sources of uncertainty;
Step 5. Define the steps in each of the four loops of the Framework required to model the sources.

The goal in step 5 is to "walk" the reader through the events in a computer model of the exposures sources that is based on the proposed Framework. Figure 12 presents the Framework with the four loops identified.

Scenario 1

Step 1. Determine what are the chemicals and sources to be considered.

The description of the chemicals in Scenario 1 is as follows.

> **Compound A and Compound B**: Semi-volatile compounds extant in common building products or coatings within a typical residence. These compounds would be expected to slowly vaporize over a period of months or years.

The compounds selected for this scenario are Texanol®[27] (2,2,4-trimethyl-1, 3-pentanediol mono 2- methyl propanoate) and ethyl glycol butyl ether (EGBE).

The exposures will include residential exposures by the dermal, oral and inhalation pathways. Some of the homes will have Texanol® in ceiling panels in the bedroom. In addition, some of the homes are assumed to be painted using a paint containing EGBE.

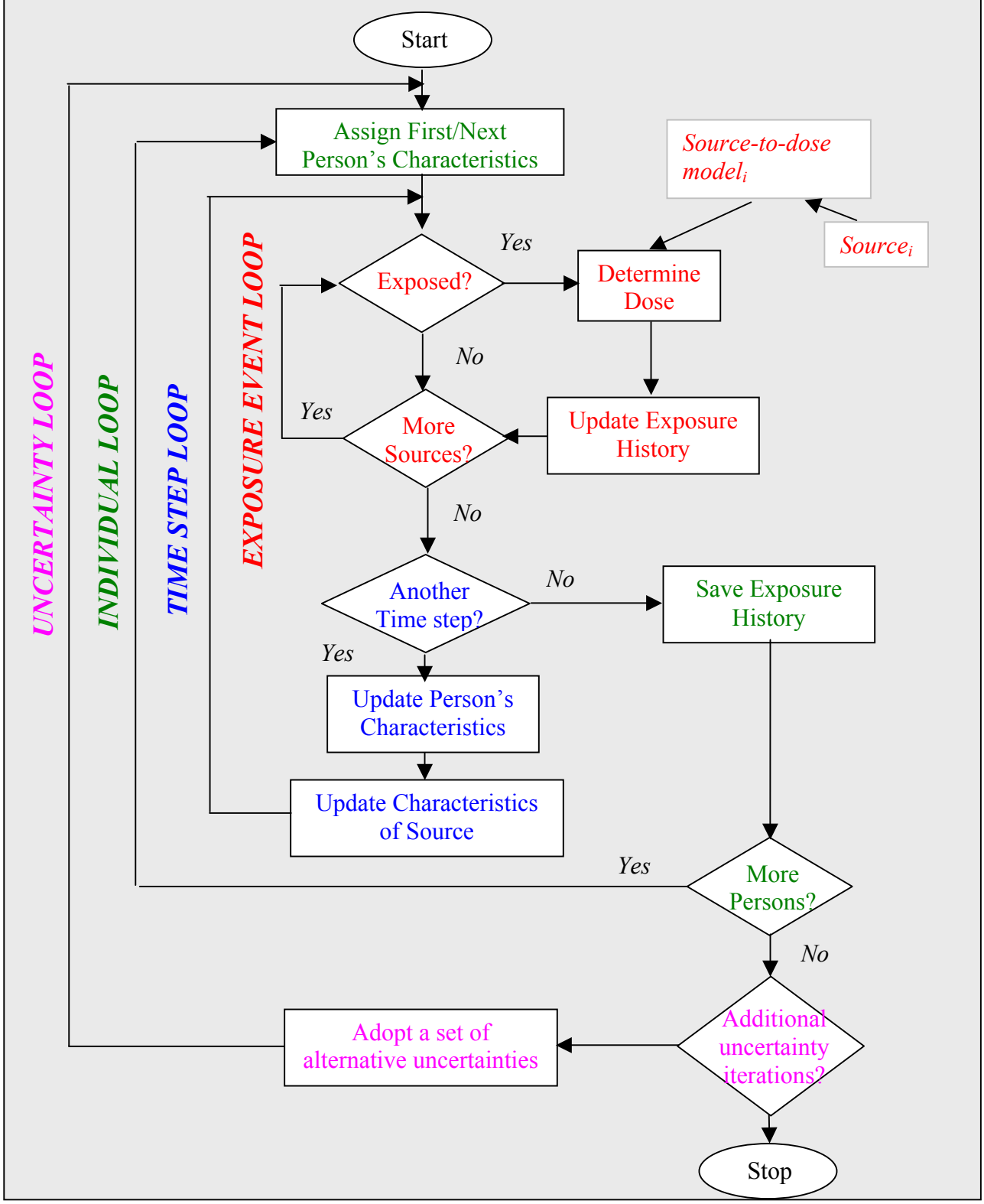
The scenario will also consider the potential for other sources of EGBE and Texanol®. Both chemicals are used in paints and it is likely that the child would be exposed to the two compounds during other painting events in the home (furniture, touch up, hobby use). In addition, EGBE is used in a wide number of cleaning products including:

- Hard surface cleaner;
- Glass/window cleaner;
- Carpet cleaner;
- Laundry detergent;
- Rust remover;
- Oven cleaner; and
- Ink/resin remover.

(Commonwealth of Australia, 1996).

[27] Texanol® is a coalescing aid used in latex paint and is not known to be used in ceiling panels; however, it is a low volatility solvent that would be released over a period of months if impregnated into ceiling panels.

Figure 11. Framework and the Four Loops: Uncertainty, Individual, Time Step, and Exposure Event



Step 2. Determine what population will be modeled and the duration of the averaging periods for the doses of interest (acute, intermediate, or chronic)

The population to be modeled is children who are exposed *in utero* from conception to birth and then up through age six. This definition of the population of concern raises questions on what is the most appropriate measure of exposure and dose for the developing fetus.

In an actual analysis of these chemicals, the approach for modeling the fetus would be determined by the form of the dose in the hazard identification and dose response portions of the assessment. If the maternal dose is the basis of the toxicity model for the compounds, then the dose to the mother should be modeled. If the dose metric for the compound is the dose to the fetus, the exposure history along with relevant physiological parameters would be fed to a separate PBPK model (that would be outside of the Framework) for estimation of resultant dose to the fetus.

In this scenario, we will assume that the relevant measure of exposure to the fetus is the dose received by the mother in mg/kg/day. As stated above, the doses to the child will be evaluated using three metrics- peak day, peak 30 day average, and average over years 0-6. The dose to the mother will also be calculated using these metrics. However, the chronic dose will be the 270-day average dose that occurs during her pregnancy.

Step 3. Determine the source-to-dose models required for each of the sources and routes of exposure and the model inputs that are required by each of the source-to-dose models.

Exposures to the two chemicals will occur while the expecting mother and child are in the home and when consumer products such as paint and hard surface cleaners are being used. Exposures to Texanol® will occur from inhalation (dermal contact with ceiling panels is assumed to be minimal). Exposure to Texanol® will also occur from minor uses of paint containing the compound. Inhalation exposure to EGBE occurs from painting and various consumer products. Dermal and oral exposure to EGBE is would occur from contact with painted surfaces and surfaces recently cleaned with hard surface cleaners. Moreover, there is a possibility of hand-to-mouth transfer for volatilized EGBE that may have sorbed to dust particles, and other more obscure pathways.

The determination of inhalation exposure is driven by three factors,

- Duration of time exposed;
- Inhalation rate; and
- Air concentration.

The relative air concentration will be a function of source location, chemical mass in the source, local mixing and transport throughout the house, and adsorption to and desorption from indoor sinks, and possibly chemical reactions. For Texanol®, the emission source is

located in the mother's bedroom suggesting that the air concentration will be higher there than elsewhere in the house. EBGE emissions can occur throughout the house as a result of human activity. Thus, mass-transfer models, fate and transport models, and chemical transformation models that reflect such physical and chemical processes, would need to be developed, adapted or adopted. Various submodels along these lines will need to be tailored to factors such as chemical properties, housing characteristics, and consumer product usage patterns. Additional data needed to support the model will include factors such as relative loading and likelihood of using ceiling panels.

The "source-to-dose" model needed to model the inhalation exposure will need to translate these data on the sources of the chemicals into time histories for chemical concentrations in the various rooms in the house. The indoor air model will need to be able to take advantage of the description of the house specified for the person. Inhalation exposure will be a function of the duration and nature of child's activities in the different locations in the house. This will require models of activity patterns that specify where the child or mother spends time and what are the activities. Finally, the model will need to translate inhalation exposure into absorbed dose by considering factors such as inhalation rate and other physiological parameters. From the age of zero to six, many of these parameters will change dramatically as the child ages.

Oral and dermal exposure will be driven by the dislodgeability of the chemicals from surfaces and the behaviors of children and pregnant women. Models of dermal and oral exposure are not well developed and are undergoing continual revision. Therefore, it is difficult to specify the factors that determine dermal and oral exposures. Factors that have been suggested include:

- The mass of residue that can be dislodged from a given area;
- The location of the residue (walls, countertops, or furniture);
- The size of the area treated;
- The age of the person;
- Their surface area and other physiological data;
- Clothing;
- Duration of time spent in a location; and
- Macro description of the activities performed in the location.

Step 4. Identify sources of uncertainty

Many of the models have inputs that have a large amount of uncertainty. In addition, uncertainty occurs in monitoring or survey data because of the potential for bias, analytical limitations, and from the limited sample size. Model inputs that are uncertain include:

- The emission rate of Texanol® from the ceiling panels;
- The reduction in dermal exposure due to clothing;
- The dislodgeability of Texanol® and EGBE from the surface of latex paint;
- The frequency of use of EGBE products;
- Incidental oral ingestion rates in adults.

Step 5. Define how the modeling would be performed under the Framework.

In the Framework, all modeling is performed in one of the four loops of the Framework, the exposure-event loop, the time step loop, the person loop, and the uncertainty loop[28]. The first loop that is triggered is the individual loop.

The Individual Loop

At the very beginning of this loop, the model selects the first mother and assigns her exposure-related characteristics. The age of the mother is selected based on the demographics data on the age of women in the U.S. who become pregnant. The woman's physiological characteristics are assigned based on physiology data of women of that age in the general U.S. population[29]. A geographical setting for the woman is established and the characteristics of the type of home that she lives in are assigned using surveys such as the American Housing Survey. (Some but not all of the women will live in the type of home specified in the scenario). The description of the home will include room sizes and the range of air exchange rates that occur over the year. The air exchange rates will vary from day to day, reflecting variation in door and windows being opened, and meteorological conditions. The structure of the woman's family is also defined. (Are there other adults in the home or other children?) Finally, the model assigns a day of the year and a day of the week for the first day of exposure. Once the exposure related characteristics of woman and her home are established, then the event loop is triggered to estimate the first day of the women's exposures.

The Exposure Event Loop

For this scenario, the time step is defined as a single day. Within that day; however, there are a number of separate exposure events. The event loop moves the woman through these events. The events are defined as blocks of time where a specific activity is performed in a specific microenvironment. Modeling these events will require data on the woman's activities. This data must be internally consistent (the model can not place her in two places at once or spend more than 24 hrs in a day in the activities). The data could come from activity pattern databases such as the combined human activity database, CHAD[30]

On this day for this individual, the first exposure event is sleeping in the bedroom with the treated ceiling panels. The dose is determined based on the length of time the woman sleeps in the room, her resting breathing rate, and the average air concentration. The average air concentration is in turn a function of the release rate of the Texanol® from the ceiling panels, the ratio of ceiling area to room volume, air mixing, and the room's air

[28] The first loop actually triggered is the uncertainty. However, for clarity discussion of uncertainty is deferred to the end of this section.
[29] If the woman becomes pregnant then the physiological changes induced by pregnancy can be modeled.
[30] See http://www.epa.gov/chadnet1/

exchange rate. The woman's breathing rates are estimated based on her age, height and body weight, and activity level (resting) using the approach of Layton (1992)[31]. Because she is sleeping, there are no dermal or oral exposures. The air concentration is determined based on the home's characteristics and indoor air modeling. The inhalation dose for Texanol® is then determined. If there is EGBE in the bedroom air, the dose from inhalation of EGBE is also determined.

Once the doses from the first event have been determined, they are saved. Then the event loop moves the woman to the next event. This event is the next activity in the next microenvironment (bathroom or kitchen or other room) during the day. During this event, the woman's activity in the microenvironment is used to derive her breathing rate and the potential for her to come into dermal contact with surfaces with dislodgeable residues of the two chemicals. The description of her activity is also used to determine if she uses a product containing EGBE (a hard surface cleaner or paint) or Texanol® (latex paint). If she comes into contact with residues of either chemical then the dermal and oral (from unintended hand to mouth contacts) are determined.

The Texanol® in the bedroom ceiling panels is assumed to be present in the other indoor microenvironments thus in this second exposure event inhalation exposure to Texanol® does occurs and an inhalation dose of Texanol® is calculated.

If while in this microenvironment, the woman uses a product containing EGBE or Texanol® (painting children' furniture or using a hard surface cleaner), the dermal, oral, and inhalation exposures that occur during this use are determined using consumer product exposure models. These models require data on the room size, the amount of the chemical used and the nature of the product.

The probability of using the products is determined using data on frequency of use of paint and other EGBE containing products.

The woman may also encounter the EGBE and Texanol® in a microenvironment that occur because of other household members activities. For example, another adult may use a hard surface cleaner and introduce EGBE into the bathroom or kitchen. Therefore, the model will determine if other persons in the home have used products that influence the woman's exposure.

This process is repeated until all of the exposure events in the first day are modeled. At that point the sum of the route specific doses of EGBE and Texanol® are determined and saved. These would be:

Total day's oral dose EGBE
Total day's oral dose Texanol®
Total day's inhalation dose EGBE
Total day's inhalation dose Texanol®
Total day's dermal dose EGBE
Total day's dermal dose Texanol®

[31] The Layton 1992 model was not developed for gravid females. This is an additional data gap.

The exposure event loop then ends and the time-step loop is triggered.

Time Step Loop

In the time step loop, the characteristics of the woman, her daily activities, and the characteristics of her home are modified to reflect day-to-day variation. For example, if the new day is a Saturday, the model will assign activities that reflect a non-workday. These could include spending more time at home, a greater likelihood of cleaning or painting and using a product that contains one or both of the two products.

The woman's characteristics would also change slightly. She would now be carrying a day old fetus and may have gained a small amount of weight.

The house's characteristics would also change. The room sizes are constant but the air exchange rates may differ if the meteorological conditions have changed, a window has been opened, a ventilation fan is used, or if there is more traffic in and out of the home. The release rate of the Texanol® from the ceiling panels would have decreased (assuming the amount released is a function of the amount remaining in the panels, and is not strongly influenced by variations in air flow through the room). The EGBE from the prior or new day's use of a hard surface cleaner may have raised the air concentration of the chemical.

Once these changes have been made, the model returns to the exposure event loop to model the next day's exposures. This process is repeated until the child is born.

At the birth of the child, the model exports the data on the mother to a database. The peak 1- day and 30-day doses and the 9-month average daily dose are calculated and saved.

At this point, the model now shifts and models the exposure to the child and not to the mother. This process begins by assigning the birth characteristics of the child based on the race and ethnicity of the mother and father. These characteristics include gender, birth weight, breathing rate, and first day's activity pattern.

The time step loop will then trigger the exposure event loop for the child's first day. The exposures are determined based on the microenvironments the child passes through on that day. As a newborn, the majority of time is spent sleeping and eating. Thus, the exposures would be almost entirely by the inhalation route[32]. Once the exposure calculations are completed for the day, the exposures are saved.

The time step loop models the child on each day until the child reaches the age of six. Each day the child's body weight, resting inhalation rate, hand size, and total surface

[32] EGBE is rapidly metabolized and is not believed to occur in breast milk. However, if this pathway was important then the mother along with the child would be modeled and the concentration in the breastmilk would be calculated using PBPK.

areas increase. As the child grows, activity patterns are modified to reflect the acquisition of new behaviors (crawling, teething, etc.) and changes in lifestyle (daycare, school, time spent out of doors, etc.).

At the end of the six years, the model stops the daily modeling and determines the peak 1 day, 30 days doses. The output for the modeling of the first child will be six doses:

1. The highest single day dose experienced by the mother during her pregnancy.
2. The highest 30-day average daily dose experienced by the mother during her pregnancy.
3. The average daily dose experienced by the mother during her pregnancy.
4. The highest single day dose experienced by the child during the first six years of life.
5. The highest 30-day average daily dose experienced by the child during the first six years of life.
6. The average daily dose experienced by the child during the first six years of life.

For each of these doses periods the model will estimate:

1. Total oral dose EGBE
2. Total oral dose Texanol®
3. Total inhalation dose EGBE
4. Total inhalation dose Texanol®
5. Total dermal dose EGBE
6. Total dermal dose Texanol®

Thus for each person there will be 36 doses[33]. Once the doses are calculated and stored, the time step loop ends and returns the model to the person loop.

The person loop then repeats the process for the next person. Once all of the persons are modeled then the model moves to the uncertainty loop.

Uncertainty Loop

In this loop, the model varies the parameters in the source-to-dose models and in the characterization of the persons. For example if the rate of emission of Texanol® from the ceiling panels is uncertain then alternative values for the emission rate are selected in this loop and the model of the population is repeated.

Scenario 2

Step 1. Determine what are the chemicals and sources to be considered

[33] Notice that if the total toxicity of the two compounds was determined to be given by a weighted sum of the two doses (a toxicity equivalent approach) then the sum of the weighted doses could also be tracked for each day. This approach has been used by EPA to evaluate the organophosphorous pesticides using Calendex™, LifeLine™ and CARES™.

The second scenario is for two semi-volatile compounds from Compound Group C from 0 to 18 years. This group is defined as:

> **Compound Group C:** A series of semi-volatile compounds of a homologous structural series present in plastics that are used or present in the home. Plastics could be part of the building materials used in the home or part of furniture. This compound would also be in objects that could also come into contact with food or children's toys.

The project team has selected two phthalates for this scenario, Diisononyl phthalate (DINP) and Dibutyl phthalate (DBP).

DINP is largely used in soft plastic products including children's furniture and toys. DBP is used in cosmetics and as a plasticizer in shower curtains, raincoats, food wraps, bowls, car interiors, vinyl fabrics, floor tiles, and other products (ATSDR, 1990; 2002). Dermal, oral and inhalation exposures are possible for both compounds; however, dermal and oral exposures are expected to be more important. This scenario will only model the dermal and oral exposures.

Step 2. Determine what population will be modeled and the measure of dose that is of interest.

The population of concern is children from birth to age 18. Dose metrics will be the same as those used in Scenario 1.

Step 3. Determine the source-to-dose models required for each of the sources and routes of exposure and the model inputs that are required by each of the source-to-dose models.

Given that this scenario involves semi-volatile chemicals being emitted from solid objects (plastics), inhalation is not expected to be a dominant exposure route. However, the types of products of concern here have emission patterns and behavior not unlike that for ceiling panels in Scenario 1. The inhalation factors discussed above in Scenario 1 apply equally here. Because inhalation exposure to low level continuous emissions was modeled in Scenario 1, this scenario will focus on the non-inhalation exposures associated with the two compounds.

Both DINP and DBP would expect to have dermal and oral exposures. The DINP oral exposures occur when small children place the toys in their mouths, Juberg et al. (2001). DBP containing cosmetics are placed on the skin or nails and in the case of facial cosmetics may be directly ingested. Finally, DBP may contaminate food from the use of plastics containing the compound. It is also possible that dermal contact will occur with other DBP containing plastics.

The exposure to DINP could be modeled in a two-step approach. First, the probability of having a DINP containing toy could be modeled based on marketing data for the products. Second, if a child has a DINP toy the probability of an exposure on a given day

can be modeled based on surveys of children's interactions with toys. Because the temporal patterns of exposure during the day are not though to be important for phthalates[34], the daily dose can be modeled based on the total time per day that the child has the toy in his or her mouth, the saliva extraction rate of DINP for plastics, and the child's body weight. Thus, even though the actual exposures occur from multiple mouthing events scattered over a day, they can be treated as a single exposure event.

A similar approach can be used for dermal exposure. Even though the child may come in contact with a number of toys or other plastic objects that contain DINP, the day's dermal exposure can be modeled as a single exposure event. Under this approach, the total amount of time a child is in contact with a surface of a DINP containing plastic, the area contacted, and the rate of transfer and the amount of DINP can be modeled each can be modeled as a single value.

Exposure to DBP can be modeled by determining the probability on a given day that the child uses makeup or comes in dermal contact with an adult using DBP containing makeup. The probability that a child uses make up will be very small for infants but does occur with young girls. Marketing data for cosmetics intended for young girls could be used to predict cosmetic use.

FDA and EPA have models of dermal absorption compounds from cosmetics (Bronaugh, 1982; EPA, 1992). These models can be used to determine the dose from use of cosmetics and from contact with individuals using cosmetics.

Finally, intake of foods containing DBP can be modeled by determining those foods that are at risk of contamination (high levels of lipids, stable during long-term storage in plastic containers). Then the levels of DBP that will be found in the foods can be modeled or measure in laboratory studies. Using this data on the specific foods that could be contaminated and the possible levels of contamination can be determined. The consumption of food has been modeled using dietary surveys (see the Initial Progress Report, August 2001). Using models or experimental data on DBP in food and the food consumption the model will seek to determine the dietary exposures during the day.

The factors that are believed to be associated with dermal and oral exposures DINP include:

- Mouthing event frequency;
- Mouthing event duration;
- Area of toy placed in the mouth;
- Dermal contact duration;
- Extraction coefficients of DINP from vinyl plastics by saliva;
- Dislodgeable fraction of DINP from plastic;
- Probability of having a DINP toy in a household; and

[34] Phthalates have low acute toxicity. Other compounds that are acutely toxic, would not average dose over time.

- Probability of playing with a toy if the toy is in the household.

For exposure to DBP in cosmetics:

- Amount of DBP in skin cosmetics;
- The amount of DBP skin cosmetic applied to skin;
- The duration of contact of the cosmetic;
- Ingestion rate of DBP containing cosmetics (lipstick and other facial cosmetics);
- Dermal absorption of DBP from cosmetic applied to skin; and
- The transfer of cosmetics to children during interactions with adults.

For exposure to DBP in foods:

- Levels of DBP in foods from use of the plastic food wraps; and
- Amount of DBP containing foods consumed.

These dermal and oral exposures differ from Scenario 1 in that they do not occur in a specific location. Children take toys with them as they move from room to room. Cosmetics by design travel with the individual. Food can be eaten in any room. As a result modeling these chemicals will require a different approach then Scenario 1.

Step 4. Identify sources of uncertainty

All of the available data in the factors identified in step 3 are subject to significant sources of uncertainty.

Step 5. Define the steps in each of the four loops of the Framework required to model the sources.

As in Scenario 1, all modeling for Scenario 2 is performed in one of the four loops of the Framework, the source loop, the time step loop, the person loop, and the uncertainty loop. The first loop that is activated in running the model is the individual loop.

The Individual Loop

At the very beginning of this loop, the model selects the first infant on the first day of his or her life and assigns her or him their exposure-related characteristics. This can be done by selecting a birth record and pulling the person's characteristics from the record. Because the sources of exposure are independent of the nature of the home, there is no need to define the child's home. Since dermal exposure will be important, the model will determine the surface area of the child. The foods the child consumes will vary by season and the model will track the season of the year. Therefore, the model will assign a day of the week and season of the year to the first day of the child's life.

Once the exposure related characteristics of the infant are established, then the event loop is triggered to estimate the first day of exposures for the child.

The Exposure Event Loop

For this scenario, the time step is again defined as a single day. Within that day, there are a number of separate exposure events. The event loop moves the child through these events. Unlike the first scenario, these events are not defined as blocks of time where a specific activity is performed in a specific microenvironment. The event are defined as interactions with the three sources of the two phthalates; playing with DINP containing toys, coming into contact with DBP containing cosmetics, and consuming foods contaminated with DBP.

The toys and cosmetic may be modeled using simple equations of dermal and oral exposure. However, foods will not have constant level of DBP. Therefore, diets will be modeled as a series of events, where each event is the consumption of a food item of a specific weight and concentration of DBP.

Therefore, the event loop will:

1. Model the dermal and oral exposure of DINP for toys and same the doses,
2. Model the dermal and oral exposure to DBP from cosmetics and save the doses;
3. Finally, model each food item in the child's daily diet to determine the oral dose (if any) from DBP (see Figure 6.)

At the end of this process, the sum of the route-specific doses of DINP and DBP from the day's exposure events determined and saved. These would be:

Total days oral dose DINP
Total days oral dose DBP
Total days dermal dose DINP
Total days dermal dose DBP

The exposure event loop then ends and the time-step loop is triggered.

Time Step Loop

In the time step loop, the characteristics of the infant, his/her daily diets, use of cosmetics, and interaction with DINP containing toys.

The time step loop models the child on each day until the child reaches the age of 18. Each day the child's body weight, hand size, and total surface areas increase. As the child grows, activity patterns are modified to reflect the acquisition of new behaviors (crawling, teething, etc.), changes in the use of cosmetics, and change in diet. During these years, the potential exposure to DINP will decline and the potential for exposure to DBP will increase.

At the end of the 18 years, the model stops the daily modeling and determines the peak 1 day, 30 day doses and the average dose to the chemicals over 18 years. The output for the modeling of the first child will be three doses:

1. The highest single day dose experienced by the child during the first 18 years of life.
2. The highest 30-day average daily dose experienced by the child during the first 18 years of life.
3. The average daily dose experienced by the child during the first 18 years of life.

For each of these doses periods the model will estimate:

1. Total oral dose DINP
2. Total oral dose DBP
3. Total dermal dose DINP
4. Total dermal dose DBP

Thus for each person there will be 12 doses. Once the doses are calculated and stored, the time step loop ends and returns the model to the person loop.

The person loop then repeats the process for the next infant. Once all of the persons are modeled then the model moves to the uncertainty loop.

Uncertainty Loop

In this loop, the model varies the parameters in the source-to-dose models and in the characterization of the persons to reflect the uncertainty in the inputs. For example, if the rate of extraction of DINP by saliva is uncertain alternative values can be used in this model.

Scenario 3

Scenario 3 is described by ACC as follows:

> The father performs various duties in the factory; however, his primary position is as a "Compounder". In this job, he performs the blending of the hydrocarbon solvent and polymer in the previously mentioned product. This requires him to sample the product every hour during the day in which his primary focus is on packing-out the product in 55-gallon drums. During a typical 8-hour workday, he will fill 10 drums per hour. Two or three times per week he is required to clean the agitator blades in the blending tank using one of the hydrocarbons present on Compound Group D as a cleaning solvent. Approximately 2 or 3 times per year there is a spill of either the cleaning solvent, compounding solvent or product with the average spill sizes of about 1, 30 and 50 gallons, respectively.

Step 1. Determine what are the chemicals and sources to be considered.

The chemicals in this process are assumed to be benzene, toluene and o, m xylenes. These chemicals are highly volatile and they co-occur in certain commonly used hydrocarbon solvents. In general, these solvents are largely composed of xylenes and toluene and only include trace levels of benzene (0.1% or less). There are four types of emissions that need to be treated: (1) Fugitive emissions, (2) agitator cleaning, (3)

product sampling, and (4) accidental spills. These source of exposure result in both dermal and inhalation exposures.

Step 2. Determine what population will be modeled and the duration of the averaging periods for the doses of interest (acute, intermediate, or chronic).

ACC defined the population as follows:

> The population to be considered for this assessment consists of the group of individuals between ages 18-65 years. Characteristic of workers in this population group can be determined from datasets maintained by U.S. Census Bureau, the Bureau of Labor Statistics, and the National Center for Health Statistics. In sampling records from activity databases, the working definition for these workers will need to be developed based on occupation/industry codes. A one-year typical exposure is the desired model endpoint of the analysis, and will be extrapolated for the period from ages 18-65.

The model will only consider male workers at this specific facility. Unlike Scenarios 1 and 2, this population will not be representative of the general U.S. population. Instead, this will be a local population of workers at a specific plant. Therefore, the model will consider the demographics of a local area. As specified in the scenario the plant is assumed to be located in northern New Jersey. The racial composition of the plant is taken from data on Franklin County in Northern New Jersey[35].

White – 55%
Black – 26%
Asian – 12.7%
Hispanic or Latino – 8.1%

The approach used in this scenario is not to model a single year but to model each year of the person's employment at the facility. There are two benefits to modeling multiple years. By modeling each year separately, the patterns of worker tenure at the plant can be modeled and the distribution of time worked at the plant can be determined. The model will use data on worker tenure from the Bureau of Labor. In addition, the model can determine if a worker with higher than normal exposures in one year will maintain the higher exposures over multiple years.

The dose metrics will be peak 1 day, peak 30 day and average dose for the years 18-65. Note the duration of the workers exposure will typically be less than 47 years since most workers change jobs and do not spend their entire careers in one facility. However, the averaging period for the chronic workers will be 47 years.

Step 3. Determine the source-to-dose models required for each of the sources and routes of exposure and the model inputs that are required by each of the source-to-dose models

[35] See. http://www.maxwell.syr.edu/campbell/nji/Franklin.htm

ACC provided the following description of the sources of exposure to the three chemicals.

> A male adult is exposed occupationally during the normal work week performing job duties that include the blending of the hydrocarbon solvent and polymer in a large blending tank, packing out the product in 55-gallon drums, taking periodic product samples, and cleaning the agitator blades in the blending tank. In addition, there is a potential exposure due to occasional job-related accidental spills. The blending operation is in the corner of a large manufacturing room and it is the only operation in the room involving the solvent. For the purposes of this discussion, it is assumed that the blending *tank, the drums, and the transfer between are closed processes with fugitive emissions. The exposure to these solvents and polymers involves exposure to multiple chemicals.*

The fugitive emission can be treated as a continual, area source. Specific emission models will need to be developed to represent the fugitive emission during the blending and transfer processes. The agitator cleaning will need to be treated as a micro-environmental exposure, differentiating the air concentration near the agitator, from concentrations elsewhere in the building. Further, there will be emissions of one or more of the chemicals of concern from the cleaner itself. Exposure during product sampling will be very brief but could be quite elevated, and will require concepts such as a "source cloud." The emissions from each of these sources will be expected to gradually decline over time, as the reservoir of available material is gradually depleted or cleaned up.

Dermal exposure to the solvent mixture will also occur during the four events. The potential for exposure will be highest for the spill events. Oral exposures are not considered in this assessment.

Factors used in the model include:

- The levels of the benzene, toluene and o, m xylenes;
- The rate of the fugitive emissions;
- Room size;
- Air exchange rates;
- The frequency of dermal contact during compounding, sampling, cleaning of blades, and spills;
- Details of the worker's assignments as the affect exposure to the four sources;
- Length of shift, and number of shifts per week; and
- Use of gloves or other protective measures.

For product spills, we would need to consider factors such as:

- The amount of the spill;
- Area affected;
- Clean-up processes;
- Possible evacuation procedures; and
- Other protective measures such as the use of respirators.

Step 4. Identify sources of uncertainty

There are major data gaps in the data on workplace behaviors. There is no general guidance or data on the variation of workers exposure across workers (Are some workers in the same job more highly exposed because of differences in behavior or physiology?) or in the same worked over time (Are exposures on one day linked to exposures on subsequent days?)

Almost no data on modeling occupational exposures were identified in the literature. While monitoring data are routinely taken in most plants, the data are not generally available and when the exposures are below the appropriate standards the data may not have been saved. Data where they do exist may be difficult to link to a specific worker.

Since each workplace's process, design, and building structure are different it is difficult to model occupational exposures on a "national" level. Unlike homes where data on residential characteristics have been evaluated in a number of national surveys (The American Housing Survey, the U.S. Census, and other smaller surveys) no surveys of workplaces have been identified in this project.

Step 5. Define the steps in each of the four loops of the Framework required to model the sources.

As in Scenario 1, all modeling for Scenario 2 is performed in one of the four loops of the Framework, the source loop, the time step loop, the person loop, and the uncertainty loop. The first loop that is activated in running the model is the individual loop.

The Individual Loop

At the beginning of this loop, the model selects the first worker and assigns him his exposure-related characteristics as of the "date of hire". Assigning these characteristics is done as a series of steps. First, the age of the person is determined from national or local data of workers ages at the date of hire. Second, the race/ethnicity of the worker is selected. If the workplace's demographics are similar to the communities, the local census data can be used (see above). Once, the age and race/ethnicity have been selected, the physiology of the person can be assigned based on national survey data such as NHANES.

Because the exposures occur at the workplace, there is no need to define the worker's home. Since inhalation exposure is the critical route, inhalation rates are calculated for the worker based on age, weight and height using Layton (1992). In order to evaluate dermal exposure it is important to determine the surface area of the worker's hands and arms. Because the workweek follows the calendar, the model will assign a day of the week and season of the year to the date of hire.

Once the exposure related characteristics of the worker are established, then the event loop is triggered to estimate the first day of exposures.

The Exposure Event Loop

For this scenario, the time step is defined as again defined as a single day. Within that day, there are a number of separate exposure events. These events fall into two categories: the ambient exposures that occur from the fugitive emissions and the shorter-term exposures during, sampling, agitator cleaning, and spill events. The first exposure event is the inhalation exposure to the fugitive emissions. This exposure occurs throughout the workday. If this level is relatively constant during the day, this exposure can be considered a single event. The other events are modeled as separate events that may or may not occur on a day.

The event loop begins by calculating the inhalation dose of the three chemicals from the fugitive releases. The loop then moves to the three types of short-term exposures. The model determines the number of sampling events that occur during a day. Once the number is determined, then each event is modeled separately (to allow for variation in exposure). If no sampling is performed on this day, the model moves on to determine if a cleaning event occurs on the day. If it occurs, the inhalation and dermal dose are determined.

Finally, the exposure event loop moves to the spill events. The model determines whether the event occurs on the day. If it occurs, the characteristics of the spill are defined these include:

- The volume of material spilled,
- The area affected,
- The concentration of the three chemicals in the material spilled;
- The time course of air levels resulting from the spill;
- Use of protective equipment;
- Resulting oral and dermal doses to the modeled worker.

At the end of the modeling of the four types of events, the model determines the inhaled dose in mg/kg[36]. The inhaled doses will take into consideration the impact of the use of protective equipment. Note the use of protective equipment based on one of the three chemicals (benzene for example) will lower the exposures for the other two chemicals. The total dermal doses in mg/kg are also calculated and saved. If no dermal contact occurs the values of these doses will be zero. Therefore the outputs of the day's exposures are:

Total inhalation dose benzene
Total inhalation dose toluene
Total inhalation dose o, m xylene
Total dermal dose benzene

[36] If desired the model could also calculate the 8 hr TWA air concentration for the three chemicals.

Total dermal dose toluene
Total dermal dose o, m xylene

The exposure event loop then ends and the time-step loop is triggered.

Time Step Loop

The first act in the time step loop is to determine of the worker continues at the plant. If the worker leaves the plant, the model ceases to model him and the time step loop ends. All workers upon reaching the age of 66 are assumed to retire and leave the plant.

If the worker does not leave, the model then updates the characteristics of the worker and the workplace. The worker would not be expected to have major changes in physiology. (There is some evident of a decline in body weight after age 40 and inhalation rates would change with age.) The physical nature of the plant would not change from day to day; however, plants are typically upgraded every 20 years (an episodic change). In addition, there may be season variations in air exchange rates due to use of heating and ventilation during certain portions of the year (cyclical change).

The exposure characteristics that would change would be the daily activities of the worker. First, there are random events that may or may not occur on each day (spills). In addition, there are the cyclic changes of the workweek (one shift per day and 5 days on and 2 days off, or an alternative pattern). There may be seasonal changes in the demand for the product that might change the activities in the plant. Finally, there are long-term trends in the demand for the plant's product that may cause overtime or layoffs. The time step loop will capture these differences. Once the work place activities have been modified, the model repeats the exposure event loop. Since the model tracks the prior activity, it is also possible to model the impact of events that occur on one day on the air concentrations of subsequent days.

When the model determines that the worker has left the plant or retired, the model stops the daily modeling and determines the peak 1 day, 30 days doses and the average dose to the chemicals over the 47 year period. The output for the modeling of the first worker will be three doses:

1. The highest single day dose experienced by the worker during his career.
2. The highest 30-day average daily dose experienced by worker during his career.
3. The average daily dose experienced by the worker during his career.

For each of these doses periods the model will estimate:

1. Total inhalation dose benzene
2. Total inhalation dose toluene
3. Total inhalation dose o, m xylene
4. Total dermal dose benzene
5. Total dermal dose toluene
6. Total dermal dose o, m xylene

Thus for each worker there will be 18 doses. Once these doses are calculated and stored, the time step loop ends and returns the model to the person loop.

The person loop then repeats the process for the next worker. Once all of the workers are modeled, then the model moves to the uncertainty loop.

Uncertainty Loop

In this loop, the model varies the parameters in the source-to-dose models and in the characterization of the persons to reflect the uncertainty in the inputs. For example, if the frequency of spills is uncertain then the frequency can be varied in this loop.

Scenario 4

Step 1. Determine what are the chemicals and sources to be considered

The chemicals in this scenario are Texanol®, EGBE and benzene. The sources of EGBE and Texanol® are the same as those in Scenario 1plus exposures to EGBE that occur in automobiles. EGBE is used in auto-air fresheners and interior-dash cleaners. Sources of benzene exposures occur in the home and the vehicle. The residential exposures include tobacco products, stored gasoline containers, lawn mowers, vehicles in attached garages, and outdoor ambient levels. Vehicular related exposures include interior levels in the car and pumping gas. The routes of exposure for Texanol® and EGBE are dermal, oral, inhalation. The routes of exposure for benzene are limited to inhalation.

Step 2. Determine what population will be modeled and the measure of dose that is of interest.

ACC described the exposed population as:

> The population to be considered for this assessment consists of the group of adults between ages 25-75 years. Some of the relevant features for ancillary databases include factors such as presence of detached or attached garage, vehicle ownership, and commuting patterns.

The exposure metrics will be the peak 1 day, peak 30 day, and the average dose for the 50-year period between ages 25 and 75.

Step 3. Determine the source-to-dose models required for each of the sources and routes of exposure and the model inputs that are required by each of the source-to-dose models

Many of the concepts discussed above for scenario one apply here. In addition, there are special conditions for two scenarios: (1) tobacco smoking, (2) emissions in garages. In the first case, we will need to consider all household and in-vehicle smoking by both the subject being modeled and other household occupants or vehicle passengers. Separate

submodels may be necessary for active and passive exposure to benzene in tobacco smoke. For garage releases, in addition to the obvious requirement for source emission profiles, information will be needed such as garage volume and air exchange rates along with air transport to and from the adjacent residence. Factors affecting Texanol® and ETBE exposure in the home will be similar to those discussed in scenario one for household products.

For in-vehicle benzene exposure, critical modeling input will include length of commuting, traffic density, vehicle air exchange rates, age and mechanical condition of the persons' vehicles. The exposure scenario while pumping gas will be akin to the "source cloud" discussed in Scenario 3 for product sampling. Factors affecting Texanol® and ETBE exposure in the vehicle also will be similar to those discussed in Scenario 1 for household products, but parameters such as air-exchange rates, volumes and product-usage patterns will need to be specific to vehicles. Limited evidence from previous studies indicates that contaminant concentrations from within vehicle sources are relatively uniform within the passenger compartment Thus multi-compartment models will not be needed in this case.

Step 4. Identify sources of uncertainty.

There are numerous sources of uncertainty in this scenario. As discussed in Scenario 1, the mechanisms of dermal and oral exposure to surface residues are poorly understood for adults. Data on autocorrelation of key behaviors such as activity patterns is quite limited.

Step 5. Define the steps in each of the four loops of the Framework required to model the sources.

As with the other three scenarios all modeling is performed in one of the four loops of the Framework, the source loop, the time step loop, the person loop, and the uncertainty loop[37]. The first loop that is triggered is the individual loop.

The Individual Loop

At the very beginning of this loop, the model selects the first adult and assigns her/his exposure-related characteristics. The age of the adult at the beginning of the model is defined as 25 years. The gender, race, and ethnicity of the adult are selected based on the demographics data for adults in the U.S. The person's physiological characteristics are assigned based on physiology data for 25 year olds of the selected gender, race and ethnicity. The model should determine if the individual is a smoker and what is the frequency of smoking.

[37] The first loop actually triggered is the uncertainty. However, for clarity discussion of uncertainty is deferred to the end of this section.

The geographical setting for the adult is established and the characteristics of the type of home that he/she lives in are assigned using surveys such as the American Housing Survey. (Some but not all of the adults will live in the type of home specified in the scenario). The description of the home will include room sizes and the range of air exchange rates that occur over the year. The air exchange rates will vary from day to day, reflecting variation in door and windows being opened, and meteorological conditions. The structure of the person's family is also defined. (Are there other adults in the home or children? Do any of the other household members smoke?) Finally, the model assigns a day of the year and a day of the week for the first day of exposure. Once the exposure related characteristics of adult and her/his home are established, then the event loop is triggered to estimate the first day of the women's exposures.

The Exposure Event Loop

For this scenario, the time step is defined as a single day. Within that day, there are a number of separate exposure events. The event loop moves the adult through these events. The events are defined as blocks of time where a specific activity is performed in a specific microenvironment. As with Scenario 1, modeling these events will require data on the adult's activities.

On this day for this individual, the first exposure event is sleeping in the bedroom with the treated ceiling panels. The dose is determined based on the length of time the adult sleeps in the room, their resting breathing rate, and the average air concentrations of EGBE, Texanol® and benzene. The adult's breathing rates is estimated based on their age and height and body weight using the approach of Layton (1992). Because the person is sleeping, there are no dermal or oral exposures. The air concentrations of the three chemicals are determined based on the home's characteristics and indoor air modeling.

Only inhalation doses for the chemicals are determined for this event. There are no dermal or oral exposures because the individual is sleeping.

Once the dose (or doses) from the first event are determined, they are saved. Then the event loop moves the adult to the next event. This event is the next activity in the next microenvironment (bathroom or kitchen or other room) during the day. During this event, the adult's activity in the microenvironment is used to derive his or her breathing rate and the potential for her to come into dermal contact with surfaces with dislodgeable residues of EGBE or Texanol®. The description of the activity is also used to determine if the adult uses a product containing EGBE (a hard surface cleaner or paint), Texanol® (latex paint), smokes, or uses a petroleum product containing benzene. If the person comes into contact with residues of EGBE or Texanol® then the dermal and oral (from unintended hand to mouth contacts) are determined.

The Texanol® in the bedroom ceiling panels is assumed to be present in the other indoor microenvironments thus in this second exposure event inhalation exposure to Texanol® does occurs and an inhalation dose of Texanol® is calculated.

The adult may also encounter benzene, EGBE and Texanol® in the second microenvironment because of other household members activities. For example, another adult may use a hard surface cleaner and introduce EGBE into the bathroom or kitchen. Therefore, the model will also determine if other persons in the home have used products that influence the adult's exposure.

The microenvironment will include the home and the vehicle related exposures. If the person enters a car, the benzene level in the car will be modeled. The model will also determine if an EGBE containing product was used in the car and if so what are the dermal and inhalation exposure that occur.

This process is repeated until all of the exposure events in the first day are modeled. At that point the sum of the route specific doses of Benzene, EGBE and Texanol® are determined and saved. These would be:

Total days oral dose EGBE
Total days oral dose Texanol®
Total days inhalation dose EGBE
Total days inhalation dose Texanol®
Total days inhalation dose benzene
Total days dermal dose EGBE
Total days dermal dose Texanol®

The exposure event loop then ends and the time-step loop is triggered.

Time Step Loop

In the time step loop, the characteristics of the adult, their daily activities, and the characteristics of her home are modified to reflect day-to-day variation. For example, if the new day is a Saturday, the model will assign activities that reflect a non-workday. These could include spending more time at home and less in a car, a greater likelihood of cleaning or painting and using a product that contains one or both of the two products.

The house's characteristics would also change. The room sizes are constant but the air exchange rates may differ if the meteorological conditions have changed, a window has been opened, a ventilation fan is used, or if there is more traffic in and out of the home. The release rate of the Texanol® from the ceiling panels would have decreased (assuming the amount released is a function of the amount remaining in the panels). The EGBE from the prior or new day's use of a hard surface cleaner may have raised the air concentration of the chemical.

Once these changes have been made, the model returns to the exposure event loop to model the next days' exposures. This process is repeated until the person reaches age 75.

At this age, the model stops the exposure event loop and determines the peak 1 day, 30 days, and 50 year average daily dose doses for the adult. For each of these doses periods the model will estimate:

1. Total oral dose EGBE
2. Total oral dose Texanol®
3. Total inhalation dose EGBE
4. Total inhalation dose Texanol®
5. Total inhalation dose for benzene
6. Total dermal dose EGBE
7. Total dermal dose Texanol®

Thus for each person there will be 21 doses.

Once the doses are calculated and stored, the time step loop ends and returns the model to the person loop.

The person loop then repeats the process for the next adult. Once all of the adults are modeled, then the model moves to the uncertainty loop.

Uncertainty Loop

In this loop, the model varies the parameters in the source-to-dose models and in the characterization of the persons. For example, the future level of benzene in gasoline may be uncertain based on proposed but yet un-adopted reformulations of gasoline. This value could be varied in this loop.

Chapter 5. Identification of Data Needs for Future Modeling

This Chapter presents a discussion of the data gaps identified during the preparation of the Framework and the application to the four scenarios. The chapter also includes recommendations for additional area of research for modeling. The following are data gaps that were identified in the application of the Framework to the four scenarios.

Behavioral data

The use of person oriented-modeling leads to a tremendous need for data about people. Questions such as:

- How well are the micro and macro behaviors that bring persons into contact with chemicals understood?
    - Time spent in micro environments
    - Breathing rates
    - Contact with surfaces floors, walls, carpet, furniture
    - Impact of clothing
    - Frequency of hand to mouth events for adults and older children
    - Hand washing
    - Frequency of use of products
    - Amount of product used at one time
- How do these behaviors vary over persons (inter-individual variation) and how do they vary over time for a person (intra-individual variation)?
- What role does a person's behaviors play in determining the magnitude of dose?

Currently data on exposure related behaviors are collected using self-reported diaries or recall surveys. The result is activity pattern data that include only macro activities descriptions and are limited to one or at most a few days. Macro descriptions of exposure in children (playing games) may be too general a description for characterizing the actual exposures (mouthing events and dermal contact. For example, "games" is a macro descriptor in NHAPS. For a three year-old child, this term could include activities that range from playing tic-tac-toe with an adult at a table to rolling on the carpet with the family pet.

As a result, alternative approaches to defining behavior should be investigated. These include electronic monitoring that either tracks an individual's locations and activities automatically over multiple days or track the interaction of the family members with an item (carpet, walls, or furniture).

Experimental designs that collect demographic data that can be used to predict the probability of performing an exposure-related behavior would also be useful. For example, if there were a high correlation between age and use of certain cosmetics that data would assist in the modeling of DBP.

Housing data

As discussed above, understanding the nation's housing is a critical factor in exposure assessments. The data on housing have been studied in diverse surveys. What is needed is an integrated database of homes where each house had data on the following factors:

- Air exchange rates,
- Room sizes,
- Water supply
- Heating system,
- Presence of pets,
- Presence of pool, garden, deck, and
- Family structure.

Much but not all of this data is collected by the American Housing Survey.

Product Data

Use of a chemical in a consumer/commercial product is the key event that determines whether a person is exposed to HPV chemicals. Very limited data are available on what products contain HPV chemicals. Stack et al. (1992) is one of the few published surveys of composition. This study is more than 10 year out of date and limited in the compounds reported (volatile organics). What is needed is a survey of HPV chemical in consumer products that would determine:

- Which HPV chemicals are in which consumer and commercial products;
- The concentration of the chemicals in the products;
- The frequency and manner that the products are used;
- Correlations of use with demographic factors that could be used to predict the probability of use; and
- The physical and chemical properties of the compound as a pure material and in products.

Modeling Needs

There is very limited data on how to model dermal and oral exposure to residues on surfaces for adults. While children are likely to have greater dermal and oral exposures then adults there are sources of exposure that are more likely for adults such as paints, cosmetics, and EGBE containing products. Existing models of dermal and oral exposures have been developed to estimate the upper bounds of doses. It is not clear how useful the models are for describing the range of doses that actually occur in a population.

THE LIFELINE GROUP

As discussed above indoor air modeling is a significant data need. While a number of indoor air models have been developed, none have the flexibility to handle the data on activity patterns, product usage, and housing characteristic data that are available. What is needed is a model that achieves the following.

1. Can be linked to models of human activities that place the modeled individual in specific rooms at specific times;
2. Can model episodic and ongoing releases of volatiles and semi volatiles in any room at any time;
3. Can make use of data on the number, type and sizes of rooms, number of floors; that a comprehensive survey of residential characteristics could generate;
4. Can make use data on family structure;
5. Can model releases related to the heating/cooling system, water use, and consumer products;
6. Generate time histories for each micro-environment during multiple days
7. Is modular and can be linked with other programs.

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Appendix A. Scenarios to be Used in Demonstrating Proposed Framework

EXAMPLE COMPOUNDS USED IN THIS PROJECT

Because of the obvious sensitivity of ACC member companies regarding the use of specific compounds in these analyses, the Technical Implementation Panel (TIP) will not specify the compounds to be used in this study. However, the TIP believes that compounds with specific chemical and physical properties must be used in each scenario if the proposed methodology is to be adequately evaluated. Consequently, the TIP has indicated in the table above (and in the descriptions below) which chemical groups or properties should be represented in each scenario. After the contract is awarded, the successful bidder will be asked to identify and use specific real world compounds within the four scenarios. Assuming that the contractor's choices match the criteria listed below, they will not be subject to review or challenge by anyone associated with CMA, the TIP, or a CMA-member company.

Compound A and Compound B: Semi-volatile compounds extant in common building products or coatings within a typical residence. These compounds would be expected to slowly vaporize over a period of months or years.

Compound Group C: A series of semi-volatile compounds of a homologous structural series present in plastics that are used or present in the home. Plastics could be part of the building materials used in the home or part of furniture. This compound would also be in objects that could also come into contact with food or children's toys.

Compound Group D: Three volatile organic compounds used in an industrial solvent based coating. At least one is a putative human carcinogen.

Compound E: A volatile hydrocarbon solvent associated with the internal combustion engine in the family's car and house.

GENERAL INFORMATION FOR THE HOME AND OCCUPATIONAL SCENARIOS:

The residence for this work is a one-story townhouse with electric heat pump with forced hot air, air-conditioned, approximately 1700 square feet, (typical modern, fairly tight, well-insulated construction) three bedrooms, 1.5 baths, in Massachusetts. The townhouse has a small grass lawn with some shrubbery that is maintained by the man of the house. The man also doses routine repair and maintenance on the interior and exterior of the residence.

A family (man 25, woman 23) moves into the home on the day following the ceiling installation and lives there for at least 20 years. The new house has new furniture and freshly painted walls with paint containing Compound B. The family has a newborn infant girl 12 months later and the mother is nursing the infant. The mother does not work and stays at home. Since age 18, the father has smoked 15-20 cigarettes per day and has worked in the occupational scenario described below.

The father's job is in a factory that manufactures a solvent-based adhesive (40%

polymer in a mixed hydrocarbon solvent – Compound Group D).

TABLE A-1. Comprehensive Chemical Exposure Framework (Framework) Summary of Proposed Scenarios to be Considered	
Scenario description	**What this scenario is designed to measure**
1. Child exposed at home to 2 chemicals (Compound A and Compound B) from conception (-9 months) to 6 years	Child exposure Multi-media, multi-pathway and multi-route exposure 2 Single chemical exposures Continuous (*i.e.,* constant)/ubiquitous source Multiple receptor behavior patterns Changing receptor characteristics over time (*i.e.,* exposure patterns will change as child grows)
2. Child exposed at home to semi-volatile compounds from Compound Group C from 0 to 18 years.	Child exposure Multi-media, multi-pathway and multi-route exposure Multi-chemical exposure Intermittent source Multiple receptor behavior patterns Changing receptor characteristics over time (*i.e.,* exposure patterns will change as child grows)
3. Adult exposed in an occupational setting (i.e., industrial plant) to multiple chemicals (Compound Group D) for one year's typical exposure and extrapolates for period from age 18 to 65.	Adult exposure Multi-media, multi-pathway and multi-route exposure Multiple chemical exposure (3 examples from Compound Group D) Exposure in multiple environments (will measure a worker's exposure through his primary job activity plus incidental exposure through other activities) Long-term, intermittent exposure
4. Adult exposed at home and in his car to two single chemicals (Compound E and Compounds A & B) from age 25-75.	Adult exposure Multi-media, multi-pathway and multi-route exposure 3-Single chemical exposure Exposure in multiple microenvironments Chronic (i.e., lifetime) exposure

SPECIFIC INFORMATION FOR EACH SCENARIO

Scenario 1 (see above- Child at home period prenatal (–9 months) to 6 years of age):

The ceilings of three rooms (kitchen, living room, dining area) are covered with a wooden strip ceiling. The porous wood was factory-treated by immersion in a saturated mineral-spirits solution of Compound A..

Similarly, the walls of the entire interior living space of house were repainted 1 week after the arrival of the new baby with standard-grade latex wall paint containing Compound B.

Fill in remaining data needs with documented assumptions.

Scenario 2 (see above – Child exposed at Home to Compound Group C):

The house has plastic furniture and wall covering that contains compounds from Compound Group C. Similarly food come into the home wrapped in plastic containing a compound from Compound Group C. Finally, there are plastic items that are played with by the child that contain compounds from Compound Group C.

Fill in remaining data needs with documented assumptions.

Scenario 3 (see above – Adult exposed in an Occupational setting)

The father performs various duties in the factory; however, his primary position is as a "Compounder". In this job he performs the blending of the hydrocarbon solvent and polymer in the previously mentioned product. This requires him to sample the product every hour during the day in which his primary focus is on packing-out the product in 55-gallon drums. During a typical 8-hour workday, he will fill 10 drums per hour. Two or three times per week he is required to clean the agitator blades in the blending tank using one of the hydrocarbons present on Compound Group D as a cleaning solvent. Approximately 2 or 3 times per year there is a spill of either the cleaning solvent, compounding solvent or product with the average spill sizes of about 1, 30 and 50 gallons, respectively.

Fill in remaining data needs with documented assumptions.

The blending operation is in the corner of a large manufacturing room (700,000 ft3). It is the only operation involving the solvent in the room.

Fill in remaining data needs with documented assumptions.

Scenario 4 (see above – Adult exposed at Home and in his Car)

The father cuts and trims the lawn with gasoline-powered equipment, works on his own car, and pumps his own gasoline.

Fill in remaining data needs with documented assumptions.