SAP Meeting Minutes No. 2002-06

FIFRA Scientific Advisory Panel Meeting
August 30, 2002

Held at the Sheraton Crystal City Hotel, Arlington, Virginia

A Set of Scientific Issues Being Considered by the Environmental Protection Agency Regarding:

STOCHASTIC HUMAN EXPOSURE AND DOSE SIMULATION MODEL (SHEDS):
System Operation Review of a Scenario Specific Model (SHEDS-Wood) to Estimate Children's Exposure and Dose to Wood Preservatives from Treated Playsets and Residential Decks Using EPA's SHEDS Probabilistic Model

/S/
Olga Odiott, M.S.
Designated Federal Official
FIFRA Scientific Advisory Panel
Date: November 13, 2002

/S/
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FIFRA SAP Session Chair
FIFRA Scientific Advisory Panel
Date: November 13, 2002

NOTICE

These minutes have been written as part of the activities of the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) Scientific Advisory Panel (SAP). These minutes have not been reviewed for approval by the United States Environmental Protection Agency and, hence, the contents of these minutes do not necessarily represent the views and policies of the Agency, nor of other Agencies in the Executive Branch of the Federal government, nor does mention of trade names or commercial products constitute a recommendation for use.

The FIFRA SAP was established under the provisions of FIFRA, as amended by the Food Quality Protection Act (FQPA) of 1996, to provide advice, information, and recommendations to the Agency Administrator on pesticides and pesticide-related issues regarding the impact of regulatory actions on health and the environment. The Panel serves as the primary scientific peer review mechanism of the EPA, Office of Pesticide Programs (OPP) and is structured to provide balanced expert assessment of pesticide and pesticide-related matters facing the Agency. Food Quality Protection Act Science Review Board members serve the FIFRA SAP on an ad hoc basis to assist in reviews conducted by the FIFRA SAP. Further information about FIFRA SAP meeting minutes and activities can be obtained from its website at http://www.epa.gov/scipoly/sap/ or the OPP Docket at (703) 305-5805. Interested persons are invited to contact Larry Dorsey, SAP Executive Secretary, via e-mail at dorsey.larry@epa.gov.

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Scientific Advisory Panel Meeting
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INTRODUCTION

The Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), Scientific Advisory Panel (SAP) has completed its review of the Stochastic Human Exposure and Dose Simulation Model (SHEDS): System Operation Review of a Scenario Specific Model (SHEDS-Wood) to Estimate Children's Exposure and Dose to Wood Preservatives from Treated Playsets and Residential Decks Using EPA's SHEDS Probabilistic Model. Advance notice of the meeting was published in the *Federal Register* on July 31, 2002. The review was conducted in an open Panel meeting held in Arlington, Virginia on August 30, 2002. Steven M. Roberts, Ph.D., chaired the meeting. Ms. Olga Odiott served as Designated Federal Official.

SHEDS-Wood was developed by the U.S. Environmental Protection Agency's (EPA) Office of Research and Development (ORD), National Exposure Research Laboratory (NERL) in consultation with EPA's Office of Pesticide Programs (OPP). Development of this scenario specific version of SHEDS followed a recommendation from the October 2001 FIFRA SAP review of OPP's proposed deterministic exposure assessment approach for chromated copper arsenate (CCA) treated wood structures. The Panel recommended the use of a probabilistic model to predict variability of absorbed doses in a given population.

All Panel members were presented with a CD containing the SHEDS User's Guide and Technical Manual, the SHEDS Software, and the annotated code. The FIFRA SAP was also provided with a case study for a hypothetical low-exposure chemical and a hypothetical high-exposure chemical to demonstrate the model interface, algorithms, inputs, and outputs. The FIFRA SAP was asked to discuss the appropriateness of the model algorithms, the selection of model input distributions for non-chemical specific parameters (e.g., activity-related factors, exposure factors), and the statistical methods used to quantify variability and uncertainty of model inputs and outputs.

CHARGE

Documentation and Operation of SHEDS-Wood

Question 1 The User's Manual for SHEDS-Wood provides installation and operational instructions for the software. The Panel is requested to comment on the clarity and completeness of the User's Manual and the organization and user-friendliness of the model interface. Does the Panel have any suggestions for improving the User's Manual or the model interface?

Question 2 The Technical Manual for the SHEDS-Wood model provides an overview of the model construct and detailed descriptions of key model components. The Panel is requested to comment on the clarity, completeness and usefulness of this document with respect to describing the model construct and scientific principles underlying the model. Does the Panel have any suggestions for improving the Technical Manual?

Question 3 The Source Code Directory on the CD provides annotated code for the exposure and dose algorithms used in the SHEDS-Wood model. Are these algorithms consistent with the descriptions in the SHEDS-Wood Technical Manual?

Model Design

Question 4 SHEDS is a probabilistic model that simulates exposure and dose for population cohorts and chemicals of interest. The model simulates individuals from the user-specified population cohorts by selecting daily sequential time-location-activity diaries from the EPA Consolidated Human Activity Database (CHAD). For this particular application of the SHEDS-Wood model, the user-specified population cohort chosen by OPP is children 1 to 6 years of age who contact playsets and/or home decks. The Panel is requested to comment on whether this approach appropriately considers demographic factors and statistical representativeness for the scenario selected, given sample size considerations for each cohort. Can the Panel recommend alternative(s) approaches to simulate a population cohort for estimating wood preservative exposure to children?

Question 5 The SHEDS-Wood model simulates longitudinal activity patterns for individuals by constructing a 365-day profile using 8 CHAD diaries from the same age-gender cohort. These eight diaries consist of two from each of the four seasons, one sampled on a weekend and the other on a weekday. The Panel is requested to comment on the appropriateness of this approach, given sample size considerations and availability of longitudinal activity data. Does the approach provide a reasonable and realistic construct with respect to temporal variability in magnitude and frequency for children's exposure to wood preservatives from treated decks and playsets?

Input Parameters

Question 6 The Panel is requested to comment on the Agency's selection of the (non-chemical specific) input values shown in Appendices 2 and 3 of the Technical Manual, especially the dermal transfer coefficient (TC) and days per year for outdoor playing, for which no data are currently available. Does the Panel have recommendations concerning the following:

A) Are there existing research (which the Agency may have missed) or recommended approaches or studies which could also be used for developing the input parameters for which few or no data are available (e.g., dermal transfer coefficient and days per year a child spends on/around treated playsets and home decks)?

B) Are the variability and uncertainty distributions assigned to these non-chemical specific input parameters appropriate?

C) Is the bootstrap approach [Frey et al. (2002)] for fitting uncertainty distributions appropriate or are there alternative approaches which are preferable?

Model Results and Applications

Question 7 The Panel is requested to comment on the statistical diagnostic tools used by SHEDS for analyzing model results (e.g., variability analyses, sensitivity analyses, uncertainty analyses) and on the model capabilities for displaying results (e.g., summary statistics tables, pie charts, CDFs). Are there additional analyses or outputs that would be useful?

Question 8 Does the Panel recommend any additional refinements or modifications to the model (e.g., equations, assumptions, or algorithms) in order to make it more relevant to this particular application?

SUMMARY OF PANEL RECOMMENDATIONS

The FIFRA SAP reviewed the User's Manual, Technical Manual and code for the SHEDS-Wood model and made suggestions for changes to improve the model. In addition the Panel made some recommendations for future research to develop data needed to reduce the uncertainty associated with model inputs. A short list of findings and recommendations follows:

1. The SHEDS-Wood User's Manual needs some reorganization, should be targeted toward users who are not familiar with SAS®, and should correct some inconsistent use of terms.
2. The SHEDS-Wood interface would benefit from added functionality to allow the user flexibility in formatting and tagging model outputs, an increased ability to specify distributions for model variables and distributions for parameter uncertainty distributions, and changes to the model's output management capabilities. Additional views were suggested to supplement the diagnostic tools currently available in the model. Finally, the Panel recommended model developers make greater provision for subgroup analysis, comparative analysis and output file export.
3. The Panel found the SHEDS-Wood Technical Manual to be generally well written, but suggested a reorganization of topics and identified a number of areas where additional discussion and clarification are needed, particularly in the areas of model assumptions and in the mechanisms and impacts of distribution truncation.
4. Members of the Panel who are familiar with SAS scripting found the SHEDS-Wood code relatively straightforward, well documented and easily checked.
5. Comparisons between the source code and the Technical Manual identified a number of areas where model assumptions are fixed in the code and/or not discussed in the Technical Manual. The Panel identified a number of these undocumented assumptions and recommended that all be documented in the Technical Manual and that some be made user-specified model inputs.
6. Regarding the use of the Consolidated Human Activity Database (CHAD) in SHEDS-Wood, the Panel felt that the developers had done a good job of using what was available but that there are limitations to the probable reality of the activity patterns generated. Not directly included in the model are some obvious stratifications of children, such as into urban, suburban, and rural place of residence, that would seem to be major determinants of children's activity patterns. The Panel recommended adding a 6 month-to-1-year cohort to the model to account for exposure in mobile but non-walking children. The Panel also discussed the need to determine whether the upper age range should be expanded to include children up to age 13.
7. The Panel discussed in detail the way the SHEDS-Wood model simulates 365-day longitudinal activity patterns, and recommended additional areas of research. In particular, Panel members were concerned with the reality of the independence/dependence in temporal patterns of activity events that is created by the method implemented in the model.
8. Additional data sources that could be used to provide inputs to the SHEDS-Wood model were identified, but in general the Panel felt that the Agency may have to take a more active approach to generating the needed information.

9. The Panel discussed the appropriateness of variability and uncertainty distributions assigned in the examples presented, and disagreed with the model developers in many places on the extensive use of the uniform distribution. The Panel identified a number of places in this complex model where the specified distributions can result in biases of overestimation and underestimation of uncertainty. Recommendations were made on standardizing the way sensitivity analyses are performed.
10. The Panel disagreed somewhat on the use of the bootstrap approach for fitting uncertainty distributions when some data are available. Some Panel members felt the method was unnecessarily complicated and could leave the user with a false sense of objectivity whereas other Panel members supported the method because of its objectivity and repeatability.
11. The uncertainty feature of the SHEDS-Wood model permits uncertainties in model input parameters to be propagated through the model to the output. Most Panelists saw this as a major advance in probabilistic exposure and risk analysis. While acknowledging that robust quantification of uncertainty will present a significant additional burden for model users, they felt that it will be worth the effort. Hence the Panel recommends further development of uncertainty analysis. Despite this, several Panelists also called for a simpler model focusing on variability analysis with sensitivity analysis.
12. Finally, the Panel made some recommendations as to future work needed to reduce uncertainty in exposure factors, including better data on the frequency and duration of child contact with treated wood structures and contaminated soils and rates of dermal (skin) transfer, the hand-to-mouth activities and saliva removal efficiency, and soil ingestion rates. The addition of physiologically-based pharmacokinetic (PBPK) models to the SHEDS-Wood model was not viewed as necessary.

MINUTES OF PANEL DELIBERATIONS

NOTE: Multiple references are made in this document to "SAS". In all cases, the phrase "SAS" will refer to the SAS® application developed by SAS Institute Inc., Cary, NC, who hold copyright and trademark registration for this product.

Documentation and Operation of SHEDS-Wood

Question 1 The User's Manual for SHEDS-Wood provides installation and operational instructions for the software. The Panel is requested to comment on the clarity and completeness of the User's Manual and the organization and user-friendliness of the model interface. Does the Panel have any suggestions for improving the User's Manual or the model interface?

PART I. USER'S MANUAL

The Panel identified positive features of the User's Manual including clear explanations of the conventions used by the manual and clear instructions for installation of and navigation within the program. The Panel also identified several potential sources of confusion, especially with regard to model constructs. These are discussed below.

The User's Manual should make it very clear that SHEDS-Wood, in its current form, will not run under SAS releases prior to V8.1.

SAS Interface

One of the biggest challenges for the User's Manual is balancing a presentation of the SHEDS-Wood application with the need for users to have a basic understanding of the SAS interface. The Panel recommends that the manual be written from the perspective of a non-SAS user and include separate sections addressed explicitly to SAS users. The Panel agreed that more detailed information should be provided to the SAS user, such as documentation on all input and output datasets, including temporary output datasets that do not appear in the View Results window. Documentation should include the name and location of each file and the names and definitions of its variables, as well as the generating procedure and the structure (i.e., what constitutes a record?) of each output file. It would not be necessary to explain the SAS interface to SAS users.

The Panel diverged on how much information should be provided to the non-SAS user. One suggestion was that the SAS interface be made as invisible as possible. Only essentials would be explained, for example, how to get back to the SHEDS-Wood menus from a SAS window, and how to close down the SAS system. However, others thought that enough information should be provided to nonusers to let them exploit some of the features of SAS. For example, more discussion could be added about the effective use of the SAS Explorer. Taking the user through a series of Explorer windows with folders containing model inputs and outputs would be helpful. The SAS Explorer can work as a tool for examining the details of a simulation by, for example, facilitating a detailed review of the daily sequence of events for each simulated individual. It allows the user to view the output file underlying a summary table. The manual should also include a description of the SAS export facility, a valuable feature that allows export of tables to Excel formats.

User's Manual organization

The manual would be improved if the chapter on the SAS user interface were moved to a separate appendix or its own chapter, preferably at the end of the manual. Such a chapter would be addressed to experienced SAS users, as noted in the preceding section.

The chapter titled "Background Topics" might better be placed in the Technical Manual, and might more appropriately be called "Background on Distributions and Sampling". Most Panel members thought the explanations of 1- and 2-stage Monte Carlo analysis in this section were very good and should be retained.

Specific sources of confusion

Most Panel members agreed that the explanations of Population Uncertainty CDFs (p. 30-31) were hard to understand. The note at the top of page 19 is misleading. It refers to excluding uncertainty for selected inputs to an uncertainty run. However, the instructions exclude both variability and uncertainty for those inputs.

Inconsistent use of terminology

The Panel noted several inconsistent uses of terms:

1) "Sensitivity" and "uncertainty" are different concepts. The terms are occasionally switched in the supporting texts.
2) "Cold/Warm Climate" is in places referred to as "Cold/Warm Weather", which is not the same thing and hence confusing.

The term "parameter" is misused throughout the User's Manual and even in the Technical Manual. The word is repeatedly used to mean two different things:

1) The defining characteristic of certain probability distributions (e.g., the mean or standard deviation of a normal distribution) that statisticians prefer to call a parameter, and,
2) An input variable in the simulation whose distribution is defined by such a characteristic. In the context of doing 2-stage stochastic analysis, where distributions of parameter values must be distinguished from distributions of input variables, it is important to use the words appropriately.

PART II. MODEL INTERFACE

Most Panel members thought there were significant advantages to developing SHEDS-Wood on the SAS platform. The speed and capacity of SAS and the enormous functionality available to experienced SAS users were mentioned. Several members, however, as well as one public commenter, thought reliance on the SAS platform was problematic. The concern centered on the cost of the license and the hardware required to run SAS, a combination that may prevent some from using SHEDS-Wood. A related concern was that the need to have the latest release of SAS might limit access even for institutions that license SAS. In addition, one Panel member stated that the model does not comply with the interface/interaction ("look-and-feel") environment users of Microsoft Windows or Apple OS applications are familiar with, and hence does not always respond as expected.

The Panel recommends that model developers identify the population of potential users of SHEDS-Wood and assess what these users think of the interface/interaction problems of a SAS-based SHEDS-Wood application. This might help direct future interface development and aid in a decision whether to move to a SAS independent application.

As regards the interface, the Panel made the following general recommendations.

1) All dialog boxes and results windows should be expandable or large enough such that vertical or horizontal scrolling to view results is not required.
2) Provide a visible indicator of the status of a simulation in progress.
3) Identify the current module and submenu with a label at the top of every SHEDS window.
4) Enable movement among program windows without going back to the main menu.

The Panel's specific comments on the interface are presented below.

Specifying model inputs

The Panel had several suggestions for the specification of input distributions.

1) Because distributions are specified in SHEDS by their natural parameters (e.g., minimum and maximum for Uniform, mean and standard deviation for Normal, geometric mean and standard deviation for Lognormal), it is not simple to investigate the effect of distribution shape on model outcomes. Under the current structure, it is difficult, for example, to change from a Uniform to a Lognormal distribution while maintaining the same mean and variance without some involved computations. A Panel member suggested using a common set of parameters to specify all distributions (for example, by their moments: three moments for some distributions, two moments in the case of a two-parameter distribution, one in the case of a point distribution). The user would only need to specify the name of the distribution and the three moments, and could easily change distributional assumptions.
2) Allow the facility to specify a Gamma, Beta, and Weibull form for the distribution of model inputs or as prior probability functions in a two-stage Monte Carlo study.
3) It would be useful to be able to specify "variability" but not have to specify "uncertainty" for selected inputs to an uncertainty run.

Several elements of the input windows were found to be confusing. The choices labeled "Variability" and "Uncertainty" in the Sampling Methods box of the Specify Model Scenario window would better be labeled "Variability Only" and "Variability <u>and</u> Uncertainty". The choices between Save and Cancel, or between Save and Exit, are confusing. In the Specify Model Scenario window, "Save" must be chosen to run anything but the default scenario, although nothing appears to be saved. In the Edit Inputs main window, "Save" actually means "save the edits permanently and continue", while "Exit" means "save the edits temporarily and continue". After editing one of the categories of inputs, the user must choose Save for the edits to have effect in the simulation, even though he/she may not want to save them permanently.

Finally, two apparent "bugs" were noted. If the user changes between "Variability" and "Uncertainty" and back again in the "Edit Inputs" dialog, some values will be reset and the user may be unaware of the changes. The Dose Factors editing window has no Save/Cancel buttons; the only way out is to close the window, which cancels the edits.

Interacting with model outputs

Panel members found several aspects of selecting results for viewing (in the View Results window) confusing. The effect of each selection needs to be defined more clearly on the screen. As presented, the items appear to function in parallel ways, but in fact work differently. Choosing a scenario narrows down the set of simulations whose results are available to the View Results function. Choosing from Variability/Uncertainty selects certain output datasets from the outputs of the selected simulations. Choosing age and gender only creates a label for the report and has no effect on what data are available. In addition, the user can select and obtain an uncertainty analysis even if the latest simulation was variability-only. This can happen if an earlier uncertainty run used the same output file name as the latest run. It might be desirable to erase all output files with the same name prefix before recreating any of them, or to warn the user in case a different output file name is desired. The "Uncertainty Analysis" window is not sufficiently self-explanatory; for example, it offers correlations but does not explain what the variables are to be correlated with, or what the Y-value is for stepwise regression.

The following comments and suggestions were made concerning the appearance of results:

1) Using "width.decimal" format, rather than scientific notation for numbers in the summary tables would make interpretation and comparisons easier. There is room in the summary tables for, e.g., a 14.10 format. This also applies to CDF plots.
2) One member prefers Box and Whisker plots to be fatter. There is an option in SAS Graph that allows the width of the box to be a function of the number of plots to be accommodated in the graph.
3) Several Panel members expressed a preference for the traditional cumulative distribution function, in which percentiles are on the Y-axis and dose is on the X-axis. The model developers may want to consider using the inverse cumulative distribution function. With this curve you see the fraction of the population above a given dose, rather than the fraction below it. On the other hand, it was noted that plots with dose on the Y-axis and percentile on the X-axis are more intuitively understandable to non-statisticians.
4) Some displays label output variables with their long explanatory names, but others use the SAS variable names, which seem unlikely to be meaningful to a user. The long names are preferred.
5) Some graphs are on log scales, others on linear scales; the user should be able to control this.

The Panel recommends that the following output-management capabilities be added:

1) The ability to keep track of the simulation specifications and modifications made to the input variables.

2) The ability to print and save all outputs including graphs.
3) The ability to view two files (input and/or output files) simultaneously without having to print them.
4) The ability to browse, rename and insert/view comments about each output file.

Finally, the following "program bugs" were noted. Pie charts are labeled "percent contribution" but the values represented are not percents. While a simulation is running, the Log button on the main SHEDS window does not work. If the SAS Log window is opened before starting the simulation, it can be reached by clicking in it, but not otherwise. In the Uncertainty Analysis subwindow of the View Results window, the "View detailed output" check box appears to have no effect.

Question 2 The Technical Manual for the SHEDS-Wood model provides an overview of the model construct and detailed descriptions of key model components. The Panel is requested to comment on the clarity, completeness and usefulness of this document with respect to describing the model construct and scientific principles underlying the model. Does the Panel have any suggestions for improving the Technical Manual?

The Technical Manual is generally well written and provides an informative summary of the SHEDS-Wood program and its application to the treated wood scenario. In fact, new users of SHEDS-Wood might be better off reading the Technical Manual before reading the User Manual. However, the explanation of 1-and 2-stage sampling in the User Manual is more understandable than that provided in the Technical Manual, which should be revised accordingly.

The sensitivity and uncertainty analyses were very helpful for understanding the key factors in the probabilistic exposure assessment. However, each of the distributions used in the uncertainty analysis should be justified on the basis of data or logical argument. Even if a distribution is based on "expert judgment", there should be some discussion of the thinking underlying its selection. It would be valuable to have several "experts" independently construct input distributions and compare the resulting uncertainty analyses. This discussion points to a need to provide within SHEDS-Wood a facility to document the underlying assumptions/data that drive a specific run of the model. Such meta data would come in useful in comparing results from multiple runs, particularly runs performed by different researchers/research groups and/or at different points in time.

The most serious deficiency of the Technical Manual is that some model parameters/assumptions are mentioned in the text, but do not appear in the discussion in the appendices nor are they part of the sensitivity/uncertainty analyses. Examples include 1) the assumption that a child is bathed every day, regardless of the Consolidated Human Activity Database (CHAD) diary entry (p.6), 2) the assumption that "the child's total bare skin surface area is covered by residue exactly once in an hour and 3) that the surface-to-skin residue transfer efficiency is 90%" (p.21). These assumptions address model inputs which should be assigned distributions (uniform or triangular) and included in the sensitivity and uncertainty analyses. The sensitivity of the model outputs to the number of diary entries sampled per year should also be evaluated.

On page 13 it is stated that the version of SHEDS does <u>not</u> separate CHAD diaries by warm and cold regions. Yet the examples presented calculate outputs based on warm or cold weather that would be considered more representative of temperate US regions rather than areas such as Southern California, Texas, Arizona, Florida, etc. In addition, the clothing habits used for the two temperature categories seem somewhat unrealistic and may not truly represent regional variations and the range of clothing habits of children. The Panel wondered whether EPA has contacted designers and distributors of preservative-treated playground structures to determine where these products are sold in order to characterize the demographics of the purchasing communities and individuals who will eventually use the structures.

The discussion on the SHEDS approach for simulating one-year activity patterns needs further expanding in the Technical Manual. Describing the process and end result with a concrete example would help eliminate misunderstandings. It is not clear, for example, if the pattern chosen for the Winter Weekday is repeated five times in a row for the 16 weeks of the winter. It is not clear what constitutes a "composite activity diary" for an individual. Also, it should clearly be stated that all events are a minimum of 15 minutes in duration and none are over an hour in duration; as appears to be the case when viewing the "profile" file in SAS Explorer. There is some indication that blood dose following a urination event is reduced, but no details are provided.

The Technical Manual should describe the order of calculations during an event. For example, it should be made clear that the dermal loading is integrated over the duration of an event (up to one hour) before absorption is calculated; thus the full dermal load at the end of the interval appears to be available for uptake at the beginning of the interval.

The discussion in paragraph 2 on page 15, regarding generation of long-term absorbed dose samples is confusing and the associated wording is awkward. It appears that the lifetime profile for each individual is constructed by stringing together six age-specific profiles, selected at random but taking into consideration the potential exposure class and gender of the individual, and then adding zero annual exposure for ages 7 to 75. It takes the reader too long to come to this understanding. Figure 8 helps, but it is on page 17, so it is not viewed until much later in the document.

The Panel noted the need for increased discussion about the mechanisms and impacts of truncation of distributions. In a number of situations, samples generated from a normal distribution are truncated to have only non-negative values. This changes the shape of the resulting sampled distribution; the ramifications of this to model outcomes are not discussed. A table presented to the Panel during the meeting showing the expected impact of truncation should be included in the Technical Manual with discussion. There should also be some discussion of what rules (if any) are used in the model to eliminate "impossible" values sampled from unbounded input distributions. If no screening occurs, this should be mentioned.

Emphasis should be placed on consistency and appropriate use of terminology. For example, one term that appears to have been misused was "case-study". Case studies involve the use of actual data and outputs are expected to provide exposure estimates for a given product. The authors were careful to note that assumed residue and soil concentrations were completely independent and different than those for actual wood preservatives. A logical next step would be a series of case-studies in which actual data are used. What is presented in the “chemical X” and “chemical Y” scenarios are “example simulations”.

Clarity could be improved by re-formatting the document in a style more consistent with a technical manual. In its current form, the manual is a hybrid of two styles, technical manual and research report. Suggested chapter titles include: Model Structure, Routes of Exposure, Sensitivity and Uncertainty Analyses, Sources and Availability of Data, Estimating and Assigning Distributions, and Model Outputs. Citations to published and unpublished studies should be included at the end of each chapter. A model structure discussion should provide figures showing iteration pathways and all necessary background on CHADS sampling strategies. The exposure section should define and in some cases address in detail all model input parameters included in Appendixes 2 and 3. Sensitivity and uncertainty chapters could be an enhanced version of what was provided at the end of the Users Manual. The limitations of available data also warrant more attention than was provided in the Conclusion section of the manual. This may be accomplished in a separate chapter in which the literature associated with data sources is reviewed.

The use of the term “parameter” (vs. variable) in the manual should be checked. Uncertainty and sensitivity are also somewhat interchanged in places. Language regarding uncertainty could be improved.

Several of the slides from the SHEDS-Wood model presentation at the meeting should be included in the manual. These include:

- The bullet stating that the robustness of the 2-stage Monte Carlo was tested by comparison of 142 uncertainty runs on 300 people with 600 uncertainty runs on 100 people.
- The figure showing an example of confidence intervals estimated with the bootstrap procedure.
- The figures showing the time course during a simulated day for calculated outputs (dermal exposure from surface residue, dermal exposure from soil, residue ingestion, soil ingestion, and cumulative total absorbed dose).

There are undocumented assumptions that can only be seen by inspecting the code, which need to be properly documented in the Technical Manual.

- Methods and impacts of truncating distributions at fixed minimum and maximum values.
- Relationships of body height to weight and surface area as extracted from the Lifeline model.

There should be an appendix documenting the input variables and the output files used by SHEDS-Woods. (Output variables are listed in the User's guide on p. 25.) Equations currently found in the Technical Manual are conceptual only and use variable names not used in SAS code. To foster understanding of the SAS code, translation should be provided. Therefore, the appendix should include a list of the input variables and a description of the files used by the program.

The Technical Manual (p. 17) mentions using stepwise regression on all of the output observations from the sensitivity analysis to rank parameter sensitivities for the variability-only runs. This analysis needs to be more fully explained. It was not clear whether a true “multivariate stepwise regression” was performed. This would imply that the stepwise regression is performed on a multivariate response vector (e.g. playset surface dermal dose, playset soil dermal dose, deck surface dermal dose, deck soil dermal dose) and contributions of model variables to the joint distribution of the response vector is being assessed. It was deemed more likely that a number of univariate stepwise regressions were used to assess input variable importance. Stepwise regression uses multiple predictors and hence is sometimes referred to as multiple stepwise regression. The term multivariate typically is used to refer to the situation with multiple responses. One does not “conduct uncertainty estimates”. One may “perform an uncertainty analysis” or “use 2-stage Monte Carlo sampling to assess parameter uncertainty on estimated dose parameters”.

The Technical Manual (p.20) states that both days per year and minutes per day children spend on and around playsets and decks were estimated using the Child-Specific Exposure Factors Handbook and SAP recommendations. Appendices 2 and 3 indicate that only days per year were estimated in this way. The text on p.14 suggests that minutes per day are estimated from the CHAD diary and a user judgment regarding the fraction of outdoor time in the vicinity of a playset/deck.

The assumed residue and soil concentration distributions for the two exposure scenarios (chemical X and chemical Y) should be provided where they are mentioned on p.20. It is important for understanding the results in Tables 1-5 and Figures 9-16 to know that in both scenarios the deck residues are assumed to be about 5 times the playset residues and that the residues in scenario Y (warm) are about 5 times the scenario X (cold) residues.

The explanation of Figure 17 is confusing. The interpretation of this type of uncertainty plot is explained more clearly in the User Manual. The text in the Technical Manual states that the three CDFs are the results for a low-, medium-, and high-dose population, which implies that the CDFs are distributions of variability rather than uncertainty. Based on the explanation in the Users Manual, they would be better described as the CDFs for low, medium and high estimates for each individual.

The definitions and units of $C_{soil,e}$ and $S_{adh,e}$ are missing from the notations list on p.48.

The format of Figure 7 (p. 16) is not consistent with output from the current version of the model. Graphics in user's manuals are typically more understandable if they do not differ from what users see when they actually run the examples for themselves.

The format of the appendix table needs improvement. It is difficult to read and comprehend.

Question 3 The Source Code Directory on the CD provides annotated code for the exposure and dose algorithms used in the SHEDS-Wood model. Are these algorithms consistent with the descriptions in the SHEDS-Wood Technical Manual?

It is not reasonable to expect the Panel to review and proof the entire code in the context of this review. EPA should not assume that such a proofing has occurred. While not a trivial coding project, the code is relatively straightforward, well documented and easily checked.

Text files of the code were provided to the Panel on CDROM. The purpose of each file is presented as a one-line phrase. Most of the Panel would prefer more explanation. The Overview file was found to be quite useful.

Most of the source files have excellent documentation via internal comments. Some (such as IndOut.SAS) have very little but may not need much. Panel members who examined the code were typically experienced SAS users. They felt they could easily find where to modify the SAS code to change output table formats from scientific notation to width/length or the fix the box-whisker plot widths for example. This is a major benefit to the package since it means that most reasonably competent SAS programmers could maintain and modify the application to meet specific needs.

After hearing responses from Agency staff to questions regarding the manner in which dermal exposures are calculated, the computational methodology for that subset of the code does appear to be reasonable. The need for questions suggests that annotation in the code could be usefully expanded. (Multiplication of surface residue by a flat fractional absorption is acceptable if time increments are 1 hour or less. Inclusion of carryover of dermal load is a noteworthy advance.)

Most of the computations are done in mdl_cal_as.sas. There are a number of hard-coded equations for growth (height, weight, total surface area) that are not documented in the Technical Manual. In general the dose equations from pages 48-49 seem to be properly implemented in the code. Occasionally, reviewers noted things in the code that did not seem to be documented in the manuals and which represented assumptions on the part of the developer. For example, it seems that no hand-to-mouth events are allowed when the child is sleeping. The activity level classification is implemented as a probability vector which specifies probabilities of selecting the top middle or bottom third of a group with regard to outtm_hr variable. It is assumed that this means that if a child is classified as a high activity level individual, his/her profile has a 0.6 probability of coming from the top third of the group. It is not clear why this was designed this way. This seems to imply that a high activity child can actually get the profile of a low activity individual.

```
* Set the probability of picking from the top, middle;
* or bottom third of group (with regard to outtm_hr);
%if (&act = h) %then %let probs = 0.6,0.2,0.2;
%if (&act = m) %then %let probs = 0.2,0.6,0.2;
%if (&act = l) %then %let probs = 0.2,0.2,0.6;
* Activity level (h,m,l) determines whether we are picking from;
* the top, middle, or bottom third of the group with;
* regard to the activity level;
* If 'a', or anyone was specified we ignore activity levels;
```

Model Design

Question 4 SHEDS is a probabilistic model that simulates exposure and dose for population cohorts and chemicals of interest. The model simulates individuals from the user-specified population cohorts by selecting daily sequential time-location-activity diaries from the EPA Consolidated Human Activity Database (CHAD). For this particular application of the SHEDS-Wood model, the user-specified population cohort chosen by OPP are children 1 to 6 years of age who contact playsets and/or home decks. The Panel is requested to comment on whether this approach appropriately considers demographic factors and statistical representativeness for the scenario selected, given sample size considerations for each cohort. Can the Panel recommend alternative(s) approaches to simulate a population cohort for estimating wood preservative exposure to children?

The question of the statistical representativeness of the use of the CHAD database in the SHEDS-Wood model has several dimensions. The first and simplest is whether the model can adequately reflect the age, gender and geographic distribution of the children in a chosen target population. CHAD compiles data from multiple studies. Only two of the data bases listed on the CHAD web site, NHAPS and the University of Michigan study, are national in scope. Neither of these is longitudinal. Since the CHAD database is a compilation of time activity diary data from multiple studies, it does not guarantee self-weighting representation of a specific national, regional or local target population. Standardization of the observed diary data to the age and gender distribution of a national or regional population requires a post-stratification weighting to U.S. Census or other source of accurate estimates of population distributions (e.g. Current Population Survey, National Health Interview Survey). This weighting adjustment is not difficult to perform. Therefore, the major challenge in using the CHAD data to model a "population" probably does not lie in producing results that have the correct age and gender proportions.

For individual children of a given age and gender, CHAD provides critical time diary data for one day observation periods. These data are needed for the SHEDS exposure model just as the Continuing Survey of Food Intake by Individuals (CSFII) data are needed in other applications to model dietary intake of foods. What these one-day "snap shots" into children's lives do provide is a picture of how a boy or girl of a specific age spent a random day in their life. The CHAD data cannot answer the question of whether the SHEDS-Wood procedure of drawing four independent seasonal pairs of week day and weekend diary observations achieves sufficient representation of the variation and correlation in a child's annual exposure pattern. Neither can the CHAD data alone guarantee that the SHEDS-Wood model is correctly representing the target population's many conditional distributions (that is, given their age and gender) for geography, climate, likelihood of contact (home type, school and preschool attendance, use of parks and areas with structures, etc.), and personal exposure-related behaviors. A simple post-stratification weighting of the results to a target populations' age and gender distribution will not address this problem.

The SHEDS-Wood model addresses child behavior and general exposure risk in part by stratifying the linkage of diary inputs by outdoor activity level—high, medium, low—but unweighted CHAD data alone does not guarantee population representation of children by activity level or their likely exposure to treated surfaces. There are likely differences in playscape and deck usage patterns between urban, suburban, and rural children and perhaps for children of differing socio-economic statis (SES) and region. Children who live in urban projects are not likely to have wood decks. A survey of children's residential and nonresidential playscapes would be useful to determine the distribution of wood structures and residues that populations of children may be exposed to in their everyday life. Unfortunately, these and other external survey data on children that would permit SHEDS-Wood to improve the simulated representation of exposure-related residential, nonresidential and behavioral attributes of child populations are extremely limited at the moment.

The Panel noted that for wood preservative studies, it is important to consider including a cohort of 6 month to 1 year-old children (after babies begin to crawl) in the exposure simulations. Exposures of older children may also be important. In reviewing videos from the Minnesota Children's Pesticide Exposure Study, while the target children who played on playscapes were between 5 and 7 years old, the age range of other children who were incidentally caught by the camera appeared to cover a larger range including children who were clearly older, perhaps as much as 12-13 years old. For the older children it was a hang-out-and-talk-with-your-friends place as compared to the active and imaginative activities of younger children. In either case there is some dermal contact with surfaces. For future versions, the Agency may need to reconsider the appropriate age range for this model. Behaviors of subpopulations likely to be at higher risk (children with autism, Pica behavior, Down's syndrome, etc.) are also not well characterized in the basic model. Some additional consideration of potential exposure to high risk groups in the form of deterministic calculations would be helpful.

Question 5 The SHEDS-Wood model simulates longitudinal activity patterns for individuals by constructing a 365-day profile using 8 CHAD diaries from the same age-gender cohort. These eight diaries consist of two from each of the four seasons, one sampled on a weekend and the other on a weekday. The Panel is requested to comment on the appropriateness of this approach, given sample size considerations and availability of longitudinal activity data. Does the approach provide a reasonable and realistic construct with respect to temporal variability in magnitude and frequency for children's exposure to wood preservatives from treated decks and playsets?

This issue has some regulatory significance if risk management decisions are to be made based on the exposures estimated for particular high percentiles of the variability distributions for wood treatment and other exposures. Other things being equal, it would be expected that procedures that induce more autocorrelation in the data will lead to expectations of greater real variability in exposures from person to person, and thus greater exposures and risks for high percentiles of the exposure distribution, given comparable median exposure/risk values. The selection of 8 diaries from age-gender groups to represent a 365-day year will induce more autocorrelation in estimates of the exposure of the same individuals on different days of the year, in comparison to the selection of a new random value for each day from age-gender-day of week strata. However, it will clearly induce less autocorrelation than simply picking a single diary record to represent a whole quarter or a whole year. Thus the 8-day model choice is neither the most conservative possibility that can be imagined nor the most anti-conservative assumption. How accurately this degree of induced autocorrelation reflects what would actually be observed in true longitudinal data sets in which the same people are followed over extended times cannot be known at the present time. If variability and or high percentile exposure predictions from SHEDS are to be the basis of regulatory decision-making it is necessary to do sensitivity analysis—accompanying the 8-day/year estimates with parallel calculations in which either more or fewer diary days per year are used. This will allow EPA, pesticide registrants, and other groups to identify whether the risk drivers for a particular risk assessment could be appreciably altered by additional research that would collect real longitudinal exposure data.

The assumption that the eight diaries adequately reflect individual variability over a year or a 3-month period needs to be tested. The Panel had no specific recommendation, other than those suggested above, on how this testing could be done. It is unclear how the 8 diary model was used in the two examples (warm and cold temperature scenarios). Sampling from each of 4 seasons would, in some cases, include both warm and cold temperatures so an example that takes this into account would not be unreasonable to include.

The dataset classifies children into low-, medium-, and high- potential exposure groups, and this classification is used to provide consistency from year-to-year in such factors as the amount of time spent in outdoor locations. Statistical weights are applied to assure appropriate age and gender representation in the sample, but it is not clear whether in some scenarios the whole sample would be generated from, for example, only the high-potential group. It does not seem reasonable to allow this to happen, yet there does not seem to be anything in the model that would eliminate this possibility.

The underlying studies come from two age-group cohorts; a 1-3 age group and a 4-6 age group. Can we be certain that a high potential 1-3 year old is also a high potential 4-6 year old? This “consistency matching” has the potential to drive the upper tails of the dose distribution. A slightly different picture may be seen if we were to allow consistency in the 1-3 age group but to change it in the 4-6 age groups.

For one year old children, in both the intermediate and long term calculation, there is no increase in body weight over the 3-month or 1-year period of simulation. This assumes that an average body weight is used for the time period. Ultimately, this may be an important issue in that the body weight increases found in children of this age group also reflect the rapid growth, metabolism, and other changes specific to this age group that are not accounted for in any of the variables.

Since the simulated diaries are not specific to an individual child, there may be some independence issues that are not realistic. This simulation structure creates serial correlations in activity patterns that represent an assumption that may or may not be realistic. Other model structures, such as to not vary activity parameters for events like playing on decks and other sporadic events, use fixed patterns of activity to represent additional assumptions. Not varying activity patterns tends to extend and thicken the upper tail, but without additional data there is little that can be done to challenge this assumption. One suggestion was to use the empirical data from CHAD to develop distributions of activities over time. This allows the ability to draw activities from distributions of activities versus drawing from a particular child's activity pattern. That is, facilitate modeling activity rather than replicating activity pattern. In a similar theme, the current approach tends to hold only time outdoors constant and not fix individual preferences for playing or not playing in specific environments/equipment (i.e., a child may prefer playsets over the deck). This may cause the model to predict less long-term variability in exposures than would actually be the case. It would seem reasonable to explore the alternative model in which other parameters were held constant for a child (such as preferences for various types of play involving home or school playsets).

Finally, it is not clear how the random start date works in the model. For short-term exposures it may be better to let the simulation always start on a specific fixed date for all individuals in the simulation. Starting at uniform random dates over the year will average the exposure over seasonal differences and should inflate the variability of the results.

<u>Input Parameters</u>

Question 6 The Panel is requested to comment on the Agency's selection of the (non-chemical specific) input values shown in Appendices 2 and 3 of the Technical Manual, especially the dermal transfer coefficient (TC) and days per year for outdoor playing, for which no data are currently available. Does the Panel have recommendations concerning the following?

A) Are there existing research (which the Agency may have missed) or recommended approaches or studies which could also be used for developing the input parameters for which few or no data are available (e.g., dermal transfer coefficient and days per year a child spends on/around treated playsets and home decks)?

It was suggested that the following data sources may add helpful information for the current analysis:

1) Stuart Shalat at EOHSI, in collaboration with colleagues in Florida is undertaking a playscape exposure study in Florida. It will be more than a year before these data are available.
2) There is videotape data of 122 children from various EOHSI studies and two additional children from a pilot project. In only one of these studies, the Minnesota Children's Pesticide Exposure Study, was there videotape information on children playing on playscapes in either a park or at home. Data on the 4 out of 19 videotaped children that did use playscapes has been communicated to EPA. The 4 children observed were at the upper range of years that EPA is trying to model (5-7 years).
3) Two other videotape studies of children's activities focused on documenting child activities

during a sampled 4-hour period. Neither of these studies focused particularly on playground behavior, but on whatever the child chose to do. In the ongoing Texas border study of 60 children by Shalat et al (2002) no (activities on) wood decks or playscapes are reported. In the work of Reed et al (1999) only one pilot child used a home playscape, and none of the 10 urban children used park playscapes or decks.

4) There are data from various studies on parental estimates of daily hand washing that may provide better estimates that those used in the current EPA analysis. For dermal loading of pesticides on children's hands both the Arizona (O'Rourke et al, 2000) and Texas (Shalat et al 2002, Black et al, 2002) border studies may provide better data. The Texas study includes data on 50 children between 7 months and 48 months, with repeated observations over 6 months on 45 of the children. Hand-to-mouth activity outdoors is one of the quantified variables. It might be useful to compare this with data from Beamer et al (2002) and Canales et al (2002). These data may also be useful for assessing hand washing over a 4-hour period. The Washington group (Fenske, 2002, Kissel et al, 2002, Lu and Fenske, 1999) or David Camann (2000) may also have data they could share.

Some Panel members pointed to the opportunity to gather information relevant to select model parameters from a variety of economic groups. Affected firms in the pesticide and wood treatment industries should have data on the number of US houses with treated decks and treated wood playsets. Although such data are likely to be regarded as confidential by the firms involved, EPA could, if the data are made available, use the information to check and possibly update the model assumptions.

Another source of information on playset/home deck usage that does not involve the same likely confidentiality constraints are trade press publications for (1) the community of people who design, purchase, and market playground equipment to municipalities, (2) large corporate retailers of home playsets, and (3) lumber and hardware marketers who sell wood and supplies to contractors who build home decks. Playset/home deck usage is part of a large category of exposure-related parameters that can be termed generically "complex behavior". Such behaviors are rarely the subject of academic studies or publications in academic journals, but they are often economically important and the subject of study and professional evaluation in trade press publications. Experts/agents/salepersons must be available to advise communities and help them evaluate how much playground capacity is needed and what are expected usage levels for children from the community in the specific age ranges important for this study. These same experts should be able to shed light on differences in usage in different climates and seasons. Such information could be used to anchor estimates of population average usage rates by groups of children.

Finally, anticipating some of the data needs for the types of analyses performed in SHEDS-Wood, during the October 2001 SAP meeting concerning exposures to children from chromated copper arsenate (CCA) treated wood structures, the Panel recommended adding urine monitoring and hand wipes to a proposed field study to gather soil and wood wipe data on arsenic from decks and playsets. Such data, if available now, would go a long way towards quantitatively estimating some key input parameters whose current uncertainty is a big part of the overall model uncertainty.

B) Are the variability and uncertainty distributions assigned to these non-chemical specific input parameters appropriate?

"Appropriate" must be judged in part in the context of the regulatory decisions that will need to be made from the information—How confident can we be that the y^{th} percentile of exposure is below some specific value y_0? Doing this means that analysts need policy guidance from OPP about what percentile is appropriate in this analysis. The current orientation of outputs suggests use of nothing higher than the 95^{th} percentile whereas previous SAP discussions on models involving dietary and residential cumulative exposure (e.g., CARES, Lifeline) have considered it important to examine up to the 99.9^{th} percentile of the exposure distribution.

"Appropriate" can also be judged on the basis of technical considerations—

1) The likely fidelity of the distributional forms and parameter values chosen for reproducing real variability caused by the mechanisms that produce different exposures for different people.

2) The accuracy, completeness, and fairness of the appraisal of uncertainty provided by the uncertainty distributions.

3) The conformance of the analysis and presentation of inputs and outputs to existing Agency guidance for the conduct of probabilistic assessments.

The Superfund program has recently provided extensive guidance in this regard (USEPA, 2001). Included in the appendices are discussions of the use of different distributions to represent variability and uncertainty and the distinction between Frequentist and Bayesian views of probability. In addition, references are provided for discussion of formal procedures for elicitation of uncertainty distributions from expert informants. The authors of the guidance document represent a good internal EPA resource for future SHEDS-Wood development and application to real risk assessment problems.

The distributional forms used for variability and uncertainty in the current draft are summarized in Tables 1 and 2.

Table 1. Variability distributions used in SHEDS-Wood with reference to the page in the technical documentation where it is discussed.

Page	Uniform	Point	Triangular	Lognormal	Normal	Total
1	4					
2	2					
3	2	1				
4	2			3		
5				1	6	
6		6		2		
7	3					
8			4			
9			8			

10	5	1				
Total	18	8	12	6	6	50
%	36	16	24	12	12	100

Table 2: Uncertainty distributions used in SHEDS-Wood with reference to the page in the technical documentation where it is discussed.

				bootstrap derivation		
Page	Uniform	Point	Triangular	Lognormal	Normal	Total
1	8					
2	4					
3	3					
4	6					
5				2	12	
6				4		
7	6					
8	12					
9	24					
10	11					
Total	74	0	0	6	12	92
%	80	0	0	7	13	100

According to USEPA, 2001 (and also USEPA 1997) many of the assumptions for model variable distributions and parameter uncertainty distributions used in the current SHEDS-Wood model need to be better documented and in many cases rethought and revised. The documentation for the model must provide much more detail than that presented to the Panel in these draft documents. In particular, the analytical section needs to document the data, if any, underlying model assumptions and provide results from sensitivity analyses of these assumptions.

The Panel felt that the extensive use of uniform distributions to represent either uncertainty or variability should be discouraged in favor of parametric distributions that do not have such strictly defined limits. Distributions with defined limits should generally be used only in cases where the limits can be firmly based on physical principles. The model should also allow use of Beta, Gamma and Weibull distributions, mixtures of any of the available distributions, and the ability to establish a distribution with a spike of probability at 0. The Beta distribution includes the Uniform as a special case and is more general as the distribution of a proportion. In the technical documentation the user should be cautioned to avoid the Normal distribution for values that are known to be non-negative and positively skewed, particularly where the standard deviation is over half of the mean.

One Panel member expressed reservations about the use of a normal distribution for both the variability and the uncertainty about the mean of the surface-to-hand transfer coefficient; i.e. the surface-to-hand transfer coefficient among children is assumed to follow a Normal distribution and the mean of that distribution (its uncertainty) is also described by a normal distribution. The panelist expressed the belief that this Normal-Normal assumption for the surface-to-hand transfer coefficient could lead to substantial understatement of the uncertainty in this factor. In particular, the model as implemented had the variance of the mean surface-to-hand transfer coefficient less than the variance among children in surface-to-hand transfer factor. Given that the variance in surface-to-hand transfer coefficients is limited by the variability in hand surface area among children, this was considered highly implausible.

During previous SAP reviews of other probabilistic modeling efforts (e.g., CARES, Lifeline) Panel members have commented on the use of uniform distributions. Synopses from these past comments are given in what follows:

- Analysts often give the perceived simplicity of the uniform distribution as an important attraction for cases where there are limited empirical data. The uniform distribution, with its defined absolute upper and lower limits, unfortunately provides an opportunity for analysis to fall into a trap that a particular parameter has zero chance of having values outside the range of a limited available data set. It is completely incorrect in general to assume that the largest and smallest values in a group of 9-30 data points or fewer represents the true minimum and maximum values that the variable can assume.

- Moreover there are few cases where the mechanisms that cause measurements or estimates of exposure-related parameters to vary among people create situations where there is no greater chance of producing a case near the center of a distribution than at its extreme end (as required for the uniform distribution to be correct). Factors that cause exposure to differ from one individual to another tend to interact multiplicatively—leading, when these factors are numerous, to expectations of a lognormal distribution. When one or more categorical factors are likely to have a strong influence on exposure (e.g., wearing short-sleeved vs. long-sleeved shirts) it is desirable to create mixtures of lognormal distributions, weighted by their expected frequency, to represent the influence of those different known cases.

- The uniform distribution is appropriate in cases where (1) it is physically impossible for the parameter to take on values outside the limits and (2) there really is no greater likelihood for values close to the center of the range rather than at either end. For example, there would be no problem in using a uniform distribution to represent the day of the week that a meteor might land. However, as many of the applications in the current model for both variability and uncertainty, the uniform distribution is often selected in cases where there can be no solid assurance that the parameter cannot take on values outside the stated range. In attempting to select a defined absolute range, the analyst is very vulnerable to the psychic trap of "overconfidence". "Overconfidence" -- the general underestimation of uncertainty (assigning confidence limits that are too narrow) is one of the best documented phenomena in risk analysis. This applies to both subjective evaluations by experts and non-experts (Tversky and Kahneman, 1974; Alpert and Raiffa, 1982; Lichstenstein and Fischoff, 1977), and to supposedly "objective" numerical calculations by physicists (Shlyakhter and Kammen, 1992).

- A 1994 paper (Hattis and Burmaster, 1994) gives a series of rules and examples of mechanisms that give rise to different distributional forms. Experience and the basic idea that variability is often the result of many factors acting multiplicatively indicates that the lognormal form is most often the best choice for exposure-related data where there is limited information. Both normal and lognormal distributions have just two parameters, and are thus no more "complex" statistically than a uniform distribution (and in that sense, less complex than the three-parameter triangular distribution). Derivation of the parameters of lognormal distributions can be done if a simple range is given together with the number of independent observations that gave rise to that range. Means and other measures of dispersion, such as a standard deviation, can also be used to estimate the parameters of lognormal distributions.

Another Panel member commented that the use of a uniform distribution may well reflect a complete lack of knowledge about the input parameter but reflects an enormous amount of model uncertainty relative to the case where even a small amount of empirical data can help us to begin to focus our estimation of the true value (or prior distribution) of that parameter.

Additional comments

Where subjective estimates are the source of uncertainty distributions, it is important to take some precautions to guard against the well established bias of overconfidence—underestimation of uncertainty. Exercises are available that can demonstrate the phenomenon to the individuals who are to be the sources of subjectively-derived uncertainty distributions (e.g., Alpert and Raiffa, 1982), and the EPA Superfund Guidance document (EPA 2001) cites several helpful sources of established expert elicitation procedures (e.g. Morgan and Henrion, 1990; Hora, 1992; USEPA, 1982).

There is a difference between a sensitivity analysis and an uncertainty analysis. One Panel member expressed the view that at this stage in our understanding, sensitivity analysis is likely to be a more useful tool than formal uncertainty analysis. There is reason for concern that it is not currently known which factors of the model are most important, and the effort to characterize prior distributions for all model components may not be well spent. This Panel member believed that the uncertainty analysis may be more manageable if EPA were to reduce the model to a core of important factors (from the sensitivity analysis) and then explore the impact of variability and uncertainty factor distributions on various quantiles of the predicted exposure distribution. Other members of the SAP expressed the opinion that there is value in performing a full sensitivity analysis, even at this early stage in understanding, but would not fully support reductions of the model or the analysis approach suggested.

Because of the exposure possibilities offered by the mobility of crawling babies, some Panel members recommended adding a 6-month-to-1-year age group to the exposure analysis. A related recommendation was to consider adding exposure from direct mouthing of treated wood surfaces.

One panelist suggested that EPA consider the use of a “Poisson one-hit model” with a lognormal transfer factor to assure that no more than 100% of material deposited on the skin is absorbed, while capturing the basic lognormal expectation for inter-individual differences in absorption rates. In this model “Fraction absorbed” = $1 - e^{-kt}$, where k follows a lognormal distribution and t is the exposure time. A similar equation can be used for removal of pesticide from the hands on washing.

Finally, one panelist suggested that the SHEDS-Wood developers do sensitivity analyses by varying each parameter up or down by amounts corresponding to approximately 1 standard deviation (or to the 17^{th} and 84^{th} percentiles) rather than applying a uniform 2-fold change for parameters that have very different amounts of variability or uncertainty.

> C) Is the bootstrap approach [Frey et al. (2002)] for fitting uncertainty distributions appropriate or are there alternative approaches which are preferable?

Most of the Panel members who commented on this question were generally supportive of the Frey et al. (2002) approach, at least for capturing the statistical sampling error portion of the uncertainty. However, there was considerable concern that other aspects of the uncertainty were not being captured. Specifically, Panel members pointed out that uncertainties in the appropriate distributional form to use for a variability distribution would be missed by the Frey et al. (2002) approach. The uncertainties assessed by the simple bootstrap sampling method would not capture the effects of unsuspected measurement error and possible lack of representativeness of the group of people studied to generate the data for the target population whose exposures are the focus of the assessment.

One Panel member pointed out that since the mean of the uncertainty distribution is always equal to the mean of the input value distribution, any sampling bias in the original point estimate of that mean is ignored. It is not clear whether this is viewed by the EPA analysts in a Bayesian statistical sense as a true posterior probability distribution for the parameter or in a “frequentist” sense as an approximate sampling distribution for the parameter estimate. Given the paucity of data for estimating these parameters or their posterior distributions, it may not matter. What is important is that the SHEDS-Wood system does enable the user to specify reasonable distributional form to evaluate the influence of uncertainty in the values of input model parameters. This issue is further explored in the Panel’s response to Question 7.

It was also noted that when the parametric bootstrap method is used, the method is applied with bootstrap samples of a size that approximates the number of empirical data points used to estimate the parameters of the distribution for a model input (e.g. n=3 one year old (non-hand) dermal transfer coefficient or n=20 for two-year-old frequency of hand-to-mouth activity per hour). In such cases, the repeated bootstrap sampling and parameter estimation generates a sampling distribution for the parameter that reflects the uncertainty (primarily sampling variance) in the estimation of a point estimate from the available data. For small sample sizes, the empirical distribution from the bootstrap simulation should be compared to the assumed parametric form of this distribution to verify the approximate fit. In particular, if the SHEDS-Wood model assumed an uncertainty distribution of uniform or lognormal for a parameter, does the bootstrap distribution for that parameter also look uniform or lognormal? For larger sample sizes (e.g. n=20 to 30), by the central limit theorem this simulated “sampling distribution” should converge to a normal distribution about the point estimate regardless of the underlying distribution of the data points used to develop the sample estimate of the parameter. Therefore, as the user-specified bootstrap sample size increases, the SHEDS-Wood documentation should caution the user that the use of non-normal distributions (such as the uniform or even the lognormal) will tend to lead to uncertainty draws that are "over-dispersed" compared to the true sampling distribution of the parameter estimate. If the amount of empirical data available to the parameters of an input distribution is large (>30) an alternative to the parametric technique would be to draw the bootstrap samples (with replacement) directly from the sample of observations (the nonparametric bootstrap). Again, if the number of observations is large (> 30) this bootstrap distribution should be approximately normally distributed about the overall sample estimate.

Another Panel member suggested that using the current bootstrap procedure to define uncertainty distributions is both unnecessary and gives a false sense of objectivity. This Panel member considered the process to be somewhat complicated and to some extent arbitrary (choice of sample size), making the results of the model harder to justify. This panelist believes that it is too narrow to think of uncertainty distributions as sampling distributions; rather it would be better to conceive of them as Bayesian prior distributions. This suggests that conjugate priors would be good choices for uncertainty distributions. Conjugate priors have many advantages; in particular, they do not give inadmissible values. There was some discussion from the Panel concerning the possibility of using correlated joint distributions for the uncertainty distributions, to avoid unlikely combinations of parameters. It is worth noting that in Bayesian analysis the prior distributions are generally univariate and uncorrelated, and that correlated prior distributions do not appear to be an issue in the Bayesian context.

Another Panel member also commented on the lack of assumed correlations in the outputs of the current bootstrap procedure. In assigning prior distributions to the mean and variance of the uncertainty distribution, it is well to keep in mind the fact that the sample mean and variance are not always distributed independently of each other. This is particularly the case for non-normal distributions. He expressed concern that assuming independent marginal distributions and not accounting for correlations, a fair fraction of the mean and variance combinations generated in the uncertainty analysis may be unrealistic. Other Panel members recommended that some comparative testing be undertaken of the outputs from the SHEDS model for particular parameters against the distribution of bootstrap input values that were used to derive the fitted uncertainty parameters. This should help resolve whether the current approach of using the bootstrap model outputs inappropriately excludes correlations in the estimated means and variances for the statistical sampling error uncertainties that should be captured by the bootstrap procedure.

Model Results and Applications

Question 7 The Panel is requested to comment on the statistical diagnostic tools used by SHEDS for analyzing model results (e.g., variability analyses, sensitivity analyses, uncertainty analyses) and on the model capabilities for displaying results (e.g., summary statistics tables, pie charts, CDFs). Are there additional analyses or outputs that would be useful?

The Panel sees SHEDS-Wood as the kernel of a larger system. At this point, the Panel is only evaluating its ability to generate realistic scenarios with fixed parameters or parameters varying over prescribed uncertainty distributions. In the future, it may be used to compare different scenarios or different sets of exposure assumptions or be included as one module in a more extensive model with multiple pathways of exposure.

Setting up scenarios is very tedious and running them produces very large output files. The advantages of using SAS are evident here. Not only does SAS handle large files efficiently, it will support scripting to run series of scenarios and produce comparative summaries of the different cases. If a user chooses not to work in SAS, the output files can be exported as text files for analyses by other means. While users can in principle write scripts to meet their own requirements, most will not be experienced SAS users and the Panel recommends that the SHEDS-Wood developers make greater provision for subgroup analysis, comparative analyses and output file export.

Perhaps the SAS export function could be enabled in the file management area. File export will be straightforward in variability analyses since complete files are available in the SAS library. In test simulations, a lifetime simulation with 10 individuals generated an Excel file with approximately 20,000 rows. Its total size, ca. 11 Mb, is easily manageable with most modern computing systems. Wherever possible files that are exported should be linked to input and simulation scenario files. These could be added as pages in spreadsheet files. With uncertainty analyses, however, size may make export of the complete file problematic.

Panel members indicated they would like to be able to do some of the following:

- Generate model output for males and females, or different age groups, or different geographic regions separately; then compare the results using quantile plots, box plots, pie charts, etc.
- Extract demographic subsets from a single run.
- Change the distribution assumption for a parameter, e.g. from uniform to lognormal, while keeping the same mean and variance, and, by plotting both results on the same graph, see how the tails of the quantile plots are affected.
- Perform an efficient sensitivity analysis by generating an activity history and holding it fixed while running a factorial design on the exposure parameters.
- Examine more closely individual profiles and absorption temporal patterns to determine whether the sample generated and forming the basis for the analysis is reasonable. An associated analysis requires the ability to examine extreme patterns to see how extreme things can get.
- Allow the user to view the input file at any time, and tag all tabular or graphical output with input file and scenario information (metadata tagging).
- Have a sensitivity analysis module with a point-and-click interface that allows specification of different output parameters such as total dose by pathway.

- Base a sensitivity analysis on equal percentiles or standard deviations of the uncertainty in various parameters instead of, or in addition to, the present analysis which imposes a uniform 2X change in each parameter regardless of its particular inherent variability or uncertainty.

Panelists were divided on the value of the "2-Stage Monte Carlo" uncertainty analysis using stochastic draws from estimated or hypothetical distributions for the population parameters of the larger input model. Some felt that it is an important feature and reflects a major step forward in the ongoing development of EPA's collection of exposure and risk-assessment tools. Even though for many model parameters we have limited empirical data to use in characterizing the uncertainty distributions, we know that our point estimates or guesses about single parameter values are very likely wrong. Even if they are unbiased when averaged across populations of interest, there must be some variability in the underlying distribution of the exposure model parameter values in real exposure settings. The uncertainty feature of the SHEDS-Wood model permits the exposure analyst to assess how reasonable levels of uncertainty will affect final exposure distributions.

Several Panel members argued that if this model were to be merged with models for other routes of exposure, a smaller, simpler version without the uncertainty analysis might be preferable. They were concerned that the use of uncertainty analyses in support of regulatory decisions may be complex and difficult to communicate. They therefore recommended that an alternative model be developed, focusing on variability analysis but adding well-developed features for sensitivity analysis.

A number of recommendations were made concerning what should be reported in the analyses, and how the results should be displayed. There should be more reporting of extremes. The estimated short- and intermediate-term doses are averages for each individual, so it might be good to get the maximum short- and intermediate-term doses as well. The Summary Table report currently provides estimates of the 95th percentile and maximum; an estimate of the 99th percentile should be added. In addition to the Population Uncertainty CDFs for the 5th, 50th and 95th percentiles, it would be useful to have the minimum, maximum and 99th percentile. It would also be helpful to have 90% and 95% confidence intervals (from the 2-stage Monte Carlo analysis) for each percentile printed out because it is hard to read them off the CDF plot.

Some improvements to the graphs were suggested:

1) An option to transpose axes.

2) An option to select logarithmic or linear scales.

3) Graphs tagged with references to the input file and scenario.

4) Error bars added to the results from uncertainty analyses.

5) Comparative box plots; extremely useful tools that should only be used to compare the same measure, in the same units, under different conditions.

The tabular analyses would be easier to interpret if the user could select scientific notation or a fixed decimal place.

The value of stepwise regression in the uncertainty analysis is limited. The p-values will depend on the range of uncertainty set for the scenario and will not necessarily indicate whether a factor is important or not. Also, since there is no other source of exposure considered here, the intercept could be removed from the regression.

Question 8 Does the Panel recommend any additional refinements or modifications to the model (e.g., equations, assumptions, or algorithms) in order to make it more relevant to this particular application?

Panel members were unanimous in urging model developers to make the enhancements described in the User Manual on page 32 under the heading, "Future Modifications". This included:

- Adding an on-screen indicator for "estimated time remaining" in a simulation.
- Providing a "cancel run" button on the main screen.
- Adding print and file export functions to the "output files" menu.

It was recommended that the following also be considered:

- Provide a means of splitting output screens so that results obtained in different simulations can be viewed simultaneously.
- Automate the creation of settings for a sensitivity analysis.
- Allow user input of distributions for several model assumptions. These include the assumption that a child is bathed every day, regardless of the CHAD diary entry (p.6), and the assumption that "the child's total bare skin surface area is covered by residue exactly once in an hour and that the surface to skin residue transfer efficiency is 90%" (p.21). The number of diary entries sampled per year should also be changeable by the user.
- Update body weight and handsize more frequently than annually.

Another area of agreement with the suggestions for future work was in the need to reduce uncertainty in several exposure factors. The "Discussion" section provided on pages 44 and 45 in the Technical Manual specified the need to improve information on:

- Child behavior as it relates to the frequency of contact with treated wood surfaces and contaminated and non-contaminated soil during outdoor play activity.
- Rates of dermal transfer, in particular hand-to-mouth frequency during contact with treated surfaces, saliva removal efficiency and fraction of hands mouthed.

In the context of this discussion, Panel members emphasized that accuracy and credibility of model outputs were, in some cases, constrained by lack of input data. It was noted that:

- The current method for estimating a surface-to-skin transfer coefficient is highly uncertain.
- Object-to-mouth contact is not included in the current version of the model. EPA should investigate whether current videography data supports inclusion of mouthing of surfaces relevant to decks or playsets such as floors, railings, chair seats and backs, etc.
- The soil ingestion distribution used in the current version of SHEDS-Wood model leads to the assumption that a non-negligible portion of the population engages in what would be considered soil pica on a daily basis. Current empirical data supports the notion that some children episodically eat gram quantities of soil. While average annual intake rates for such children are not known to be particularly high, it suggests that EPA take another look at the soil ingestion distribution assumptions.
- Anecdotal information suggests the existence of specific subpopulations that may be at high risk (e.g., children with pica or Down's syndrome). Representative data characterizing behaviors of these children do not currently exist and therefore cannot easily be added to the existing model. Nevertheless some screening type calculations should be generated and included in explanatory materials.

On-going and planned research that will improve estimates of these factors was strongly endorsed. In addition, it was agreed that longitudinal activity data which can be used to verify results of CHADS sampling strategies, and a comprehensive set of measurements describing spatial and temporal variability in wood surface and soil concentrations in the vicinity of treated wood structures would reduce uncertainty and improve the quality of model exposure estimates.

The Panel disagreed with the Agency recommendation that the treated wood assessment could be improved by linking SHEDS-Wood with ERDEM to allow PBPK dosimetry. It was suggested that this approach could be misleading and might not provide any additional capability specifically for the analysis of wood preservatives and preservative residues compared to the compartmental description already provided in the model.

One Panel member also noted that elimination of the need to run on a SAS platform should be considered. Standalone and network versions of SAS are costly and may not be readily available to some members of the SHEDS user community.

Finally, it was recommended that SHEDS-Wood exposure scenarios be broadened to consider other possible routes or sources of exposure to wood preservatives. These could include contact with wood surfaces such as docks, wood siding and fences. Since some wood preservatives and/or their residues might be found in food and water, inclusion of those pathways in future versions of the model may be appropriate. In sum, the Panel identified the need to aggregate exposures.

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