February 13, 2004

MEMORANDUM

SUBJECT: Transmittal of Meeting Minutes of the FIFRA Scientific Advisory Panel Meeting Held December 3-5, 2003

TO: James J. Jones, Director
Office of Pesticide Programs

FROM: Paul I. Lewis, Designated Federal Official
FIFRA Scientific Advisory Panel
Office of Science Coordination and Policy

THRU: Larry C. Dorsey, Executive Secretary
FIFRA Scientific Advisory Panel
Office of Science Coordination and Policy

Joseph J. Merenda, Jr., Director
Office of Science Coordination and Policy

Please find attached the meeting minutes of the FIFRA Scientific Advisory Panel open meeting held in Arlington, Virginia from December 3-5, 2003. This report addresses a set of scientific issues being considered by the Environmental Protection Agency regarding a draft preliminary probabilistic exposure and risk assessment for children who contact CCA-treated wood on playsets and decks and CCA-containing soil around these structures.

Attachment

cc:

Susan Hazen
Adam Sharp
Anne Lindsay
Janet Andersen
Debbie Edwards
Steven Bradbury
William Diamond
Arnold Layne
Tina Levine
Lois Rossi
Frank Sanders
Margaret Stasikowski
William Jordan
Douglas Parsons
Daniel Rosenblatt
David Deegan
Vanessa Vu (SAB)
OPP Docket

FIFRA Scientific Advisory Panel Members

Steven Heeringa, Ph.D.
Fumio Matsumura, Ph.D.
Mary Anna Thrall, D.V.M.

FQPA Science Review Board Members

John Adgate, Ph.D.
Michael Bates, Ph.D.
Chi-Hsin Selene Jen Chou, Ph.D.
Natalie Freeman, Ph.D.
Marcie Francis, Ph.D.
Dale Hattis, Ph.D.
John Kissel, Ph.D.
Stan Lebow, Ph.D.
Peter Macdonald, D. Phil.
David MacIntosh, Sc.D.
Kenneth Portier, Ph.D.
Nu-May Ruby Reed, Ph.D.
Jim E. Riviere, DVM, Ph.D.
Barry Ryan, Ph.D.

Jacob Steinberg, M.D.
David Stilwell, Ph.D.
Miroslav Styblo, Ph.D.
Donald Wauchope, Ph.D.

SAP Meeting Minutes No. 2003-04

MEETING MINUTES

FIFRA Scientific Advisory Panel Meeting, December 3-5, 2003, held at the Sheraton Crystal City Hotel Arlington, Virginia

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

Draft Preliminary Probabilistic Exposure And Risk Assessment For Children Who Contact CCA-Treated Wood On Playsets And Decks And CCA-Containing Soil Around These Structures

NOTICE

These meeting minutes have been written as part of the activities of the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), Scientific Advisory Panel (SAP). This report has not been reviewed for approval by the United States Environmental Protection Agency (Agency) and, hence, the contents of this report 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 reports 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 Paul Lewis, FIFRA SAP Designated Federal Official, via e-mail at lewis.paul@epa.gov

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SAP Meeting Minutes No. 2003-04

Meeting Minutes:
FIFRA Scientific Advisory Panel Meeting, December 3-5, 2003, held at the Sheraton Crystal City Hotel, Arlington, Virginia

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

Draft Preliminary Probabilistic Exposure And Risk Assessment For Children Who Contact CCA-Treated Wood On Playsets And Decks And CCA-Containing Soil Around These Structures

Mr. Paul Lewis
Designated Federal Official
FIFRA Scientific Advisory Panel
Date: February 13, 2004

Steven Heeringa, Ph.D.
FIFRA SAP Session Chair
FIFRA Scientific Advisory Panel
Date: February 13, 2004

Federal Insecticide, Fungicide, and Rodenticide Act
Scientific Advisory Panel Meeting
December 3-5, 2003

Draft Preliminary Probabilistic Exposure And Risk Assessment For Children Who Contact CCA-Treated Wood On Playsets And Decks And CCA-Containing Soil Around These Structures

PARTICIPANTS

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David Stilwell, Ph.D., University of Connecticut, Connecticut Agricultural Experiment Station, New Haven, CT

Miroslav Styblo, Ph.D., Research Associate Professor, Department of Pediatrics, University of North Carolina at Chapel Hill, Chapel Hill, NC

Donald Wauchope, Ph.D., Research Chemist, Southwest Watershed Research Lab, USDA, Agricultural Research Service, Tifton, GA

PUBLIC COMMENTERS

Oral statements were made by:

Barbara Beck, Ph.D. (Gradient) on behalf of the Wood Preservative Science Council

Chris Chaisson, Ph.D. (Lifeline Group) on behalf of the American Chemistry Council

Floyd Frost, Ph.D. (Lovelace Research Institute) on behalf of the Wood Preservative Science Council

Mr. John Horton (Osmose) on behalf of the Wood Preservative Science Council

Ms. Jane Houlihan (Environmental Working Group)

Steven Lamm, M.D. (Consultants in Epidemiology & Occupational Health, Inc; Johns Hopkins University-Bloomberg School of Public Health, Department of Health Policy and Management)

Yvette Lowney, Ph.D. (Exponent) on behalf of Georgia Pacific

Barbara Petersen, Ph.D. (Exponent) on behalf of Georgia Pacific

Mike Ruby, Ph.D. (Exponent) on behalf of Georgia Pacific

Raj Sharma, Ph.D. (Arch Chemical Company) on behalf of the Wood Preservative Science Council

Leonard Smith, Ph.D. (State University of New York, ESF) on behalf of the Treated Wood Council

Helena Solo-Gabriele, Ph.D. (University of Miami) on behalf of the University of Miami, University of Florida, and Florida International University Collaborative CCA-treated Wood Research

Joyce Tsuji, Ph.D. (Exponent) on behalf of the American Chemistry Council

Written statements were received from:

American Chemistry Council's CCA Task Force

Steven Lamm, M.D. (Consultants in Epidemiology & Occupational Health, Inc; Johns Hopkins University-Bloomberg School of Public Health Department of Health Policy and Management)

Helena Solo-Gabriele, Ph.D. (University of Miami) on behalf of the University of Miami/University of Florida, Florida International University Collaborative CCA-Treated Wood Research

Carter Holt Harvey

Michele Lafantaisie (private citizen)

Andrew Wegmann (private citizen)

Wood Preservative Science Council

INTRODUCTION

The Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), Scientific

Advisory Panel (SAP) has completed its review of the set of scientific issues being considered by the Agency pertaining to its Draft Preliminary Probabilistic Exposure And Risk Assessment For Children Who Contact CCA-Treated Wood On Playsets And Decks And CCA-Containing Soil Around These Structures. Advance notice of the meeting was published in the *Federal Register* on September 26, 2003. The review was conducted in an open Panel meeting held in Arlington, Virginia, from December 3-5, 2003. The meeting was chaired by Steven Heeringa, Ph.D. Mr. Paul Lewis served as the Designated Federal Official. Mr. William Jordan (Office of Pesticide Programs, EPA) provided an introduction on the goals and objectives of the session. Halûk Özkaynak, Ph.D. (Office of Research and Development, EPA) offered an introduction to the SHEDS-Wood model assessment for CCA. Valerie Zartarian, Ph.D. (Office of Research and Development, EPA) presented a summary of SHEDS-Wood model methodology, inputs for the CCA exposure assessment and the SHEDS-Wood ADD and LADD results for the CCA assessment. Halûk Özkaynak, Ph.D. (Office of Research and Development, EPA) highlighted the strengths and limitations of the probabilistic exposure and dose assessment. Winston Dang, Ph.D. M.P.H. (Office of Pesticide Programs, EPA) provided an introduction on the goals and objectives of the probabilistic CCA risk assessment, CCA risk analysis and results. Dr. Dang concluded the Agency's presentation by highlighting the strengths and weaknesses of the probabilistic risk assessment.

In preparing these meeting minutes, the Panel carefully considered all information provided and presented by the Agency presenters, as well as information presented by public commenters. This document addresses the information provided and presented within the structure of the charge by the Agency.

CHARGE

Issue 1: Documentation, completeness, and clarity of the model source code and the exposure assessment report

Both the SHEDS-Wood source code and the probabilistic exposure assessment report have been significantly revised since the August 2002 SAP.

Question A: The Source Code Directory on the CD provided to the SAP includes 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 CCA exposure assessment report? Does the revised SHEDS-Wood version 2 code (i.e., the code submitted for the December 2003 SAP) accurately reflect changes to the version 1 methodology (i.e., the code and methodology presented to the August 2002 SAP) described in the report?

Question B: The SHEDS-Wood CCA exposure assessment report presents the model construct, selected model inputs, model results, and comparison to other CCA model estimates. Please comment on the clarity, completeness and usefulness of this document.

Issue 2. Modifications to SHEDS-Wood model code and the exposure scenarios selected
A number of modifications to the model code and scenario-specific changes have been made to the SHEDS-Wood model since the August 2002 SAP.

Question A: Considering the limitations of available information and state-of-the-art modeling methods required for the assessment of children's exposures from contacting CCA treated wood residues and CCA containing soil, are the revisions made to the SHEDS-Wood code or algorithms scientifically sound and acceptable ?

Question B: The SHEDS-Wood model has been modified using feedback from the August 2002 SAP. In particular, the recent assessment, includes: assessment of exposures of children contacting only CCA treated public playsets; sensitivity of results to changing the age group of exposed children to 1-13 years, and; a separate analysis for children exhibiting pica soil ingestion behavior. The Panel is requested to comment on the appropriateness of the new exposure scenarios in the revised probabilistic exposure and dose assessment.

Issue 3. Key input variables and specification of associated variability distributions

Sensitivity and uncertainty analyses of the SHEDS-Wood model results identified the following as key input variables influencing the model results: wood surface residue-to-skin transfer efficiency; wood surface residue levels; fraction of hand surface area mouthed per mouthing event; and GI absorption fraction for residues. In addition to the above variables, sensitivity and uncertainty analyses also indicated the importance of following additional variables: average number of days per year a child plays around CCA-treated playsets, frequency of hand washing, daily soil ingestion rate, and average fraction of non-residential time a child plays on/around CCA-treated playsets.

Question A. Has the Agency used the best available information for developing input distributions for these variables? If not, are there any other data that EPA should be aware of? Considering the limitations and uncertainties with available information, are the choices made in developing distributions for each of these key variables using the available information reasonable and scientifically sound?

Question B. In some of these instances (see Table 12, page 58), because of data limitations, the Agency has made simplifying assumptions to represent them as point estimates based on professional judgment. Are the simplifying assumptions presented in the draft exposure assessment for making these decisions adequately supported by relevant scientific data? Are the choices made to quantify these variables (i.e., selected distributions or point estimates) reasonable and sound?

Question C. Are the methods used for fitting variability distributions that are assigned to model input variables for the CCA assessment appropriate?

Question D. The Panel is requested to comment on whether any other model inputs are either key drivers of results or sources of large model uncertainty. Do these model input variables and the distributions assigned to them appropriately reflect available scientific data? Did EPA appropriately integrate the available data to derive the distributions for these input variables?

Issue 4: Methods and results for sensitivity and uncertainty analyses

EPA's draft CCA Exposure Assessment includes a formal sensitivity and uncertainty analysis as well as discussion of various sources of uncertainty in the model analyses.

Question A: The Panel is requested to comment on the utility and suitability of the statistical diagnostic tools used by SHEDS for analyzing model results (e.g., variability analyses, sensitivity analyses, uncertainty analyses).

Question B: Is the bootstrap approach that is used for fitting uncertainty distributions, which has been revised in response to prior SAP comments, implemented properly, or are there alternative approaches that are recommended?

Question C: Are the uncertainty distributions assigned to chemical and non-chemical specific model input parameters appropriate?

Question D: The Panel is requested to comment on whether the modeling approach and documentation appropriately identify and address critical sources of uncertainty in the model and the resulting exposure estimates. Does EPA's documentation adequately describe the uncertainties inherent in the data used for modeling and the influence of these uncertainties on interpretation of the modeling results?

Question E. Does the Panel recommend performing any additional uncertainty analyses to evaluate the impacts of using alternative input distributions on the modeling results (*e.g.*, to address uncertainties in various factors determining the frequency of children's exposures to CCA-treated wood in playsets and decks)?

Issue 5: Special Model Simulations

A number of special simulations with the SHEDS-Wood model were conducted in order to examine the importance of specific exposure scenarios or the impact of certain input assumptions. For example, some of these analyses included conducting separate simulations for children exposed to public playsets only, modeling exposures of the 7-13 year old age group, and studying exposures of children exhibiting pica behavior. Additional analyses were also conducted to examine the impacts of using data or assumptions about increased GI absorption, decreased dermal absorption, lowering the transferable wood residue concentrations by sealants, and hand washing after play events. The results from these special analyses were not significantly different than the baseline model results, except for the large impact of assuming the use of sealants would greatly reduce wood residues.

Question A. The Panel is requested to comment on the appropriateness of the justifications made in characterizing the key factors or inputs for each of these special simulations. Did the Agency provide adequate technical rationale and justification for its choices for these alternative exposure scenarios or input distributions? Do the results from these special analyses reflect proper use of available information?

Question B: Do any of the findings from these special analyses necessitate the Agency to consider revising certain scenarios or inputs to the baseline assessment?

Issue 6: Evaluation of the SHEDS-Wood model results

The Agency has evaluated the probabilistic CCA exposure model results by comparing them to results from other earlier deterministic CCA assessments. In particular, the SHEDS-Wood model results were found to compare well to a deterministic CCA assessment performed by the Gradient Corporation, and SHEDS-Wood upper percentiles compare well to deterministic Consumer Product Safety Commission estimates.

Question A: Has EPA provided adequate documentation of the overall plausibility of the exposure estimates generated by the SHEDS-Wood model for CCA? Are the comparisons with the results of other selected exposure assessments appropriate and appropriately presented? Are there any other types of benchmarking approaches or data to assess the reliability of the overall exposure model or specific model elements?

Issue 7: Overall completeness and acceptability of the SHEDS-Wood probabilistic CCA exposure assessment

EPA has revised the August 2002 SHEDS-Wood exposure assessment after carefully considering numerous comments and suggestions that it has received from various parties, including those from the August 2002 FIFRA SAP members, EPA/ORD and EPA Program Office peer-reviewers of the preliminary draft September 2003 report, and from the general public and other external groups.

Question A: In addition to the comments and suggestions already offered by the Panel members under the specific issues raised previously, considering the availability of data and information, does the Panel recognize any critical gaps in information or methodologies that still need to be addressed for the CCA exposure and dose assessment?

Issue 8: In the study by Nico et al. (2003), X-ray absorption spectroscopy (XAS) was used to determine the chemical and structural state of arsenic and chromium molecules in CCA-treated wood residue samples. Based on the results of their analysis, Nico et al. (2003) determined that arsenic and chromium formed a "chemical complex bonded to the wood structure." Based on this study, the dominant oxidation state of the two elements is As(V) and Cr(III), and the local chemical environment of the two elements is best represented as a stable Cr/As cluster consisting of a Cr dimer bridged by an As(V) oxygen ion. Nico et al. (2003) also maintained that this chemical complex was quite resistant to leaching.

Question A: The Panel is requested to comment on the Nico et. al. (2003) study and particularly on the arsenic and chromium chemical complex from CCA treated wood surface residue, and whether the Panel believes that the chemical complex is formed during the fixation process. What is the meaning of this complex cluster formation to the current risk assessment.

Issue 9. Casteel et al. (2003), reported that the relative bioavailability (RBA) of dislodgeable wood residue is 27%. This value is significantly lower than the default value of 100% that is usually employed when reliable site-specific data are lacking and also lower than the RBA value recommended by the SAP 2001. The result of this study indicates that the arsenic in the dislodgeable arsenic material is not as well absorbed as soluble arsenic.

Question A: Does the Panel agree that, in light of the Casteel study and the Nico study discussed in issue 8, the Agency should use 27% for the RBA to estimate the bioavailable dose.

Issue 10: In the 2001 SAP meeting, the Panel cited the research of Wester et al. (1993) as a source of the dermal absorption rate of soluble arsenic in water and soil. The Panel recommended using a 2-3 % dermal absorption rate for arsenic residue on the surface of wood. Recently, a preliminary study by Wester et al. (2003) that has been submitted by the same laboratory compares the dermal absorption of arsenic in CCA-treated wood surface residues with arsenic in water solution. Although the Agency has not received the complete results of this study (e.g., the recovery of the arsenic in the urine of the animal given IV dose of arsenic), the preliminary results of this study indicate that the dermal absorption of 0.01% from wood surface residue was approximately two orders of magnitude lower than the results in water. The dermal absorption from this study was based on urinary arsenic data following application of arsenic in CCA-treated wood residue that had been weathered by the environment.

Question A: Taking into consideration the Nico et al. study mentioned in issue 8, the Panel is requested to comment on whether this new study conducted by Wester et al. provides a more appropriate estimate of dermal absorption from contact with CCA-treated wood surfaces than the earlier 1993 Wester et al. study.

Issue 11: In the 2001 SAP meeting, the Panel recommended that a biomonitoring study be performed on children who are normally exposed to CCA-treated playground equipment and decks. The Panel recommended that the study should be designed according to well-accepted epidemiological principles, including adequate sample size, to resolve the issue of whether there are substantial exposures to children from arsenic residues after playing on decks and playsets. The Panel indicated data from such a biomonitoring study could be directly used in the risk assessment and could be used to validate the exposure assessment model. Recently, a proposed protocol for a pilot study was submitted to OPP for peer review; this proposed protocol is an attempt to determine if changes in exposure to arsenic can be assessed by examining changes in the urinary excretion of arsenic. EPA has provided the Panel with a copy of the proposed protocol for the pilot study. In summary, the proposed pilot study will determine whether a significant difference in urinary arsenic can be discerned when a population of children are switched from arsenic-containing tap water to an essentially arsenic-free source of drinking water.

Question A. The Panel is requested to comment on the strengths and limitations of the approach to be employed in the proposed pilot study to help resolve the issue of whether there are substantial exposures to children from arsenic residues after playing on decks and playsets. In

particular, please comment on the feasibility, the potential confounding background sources from the statistical analysis, the sensitivity and accuracy of analytical method for quantification of arsenic in urine to detect changes, the determination of intraindividual variation and interindividual variation based on the current knowledge of exposure; and any other aspects of the proposed pilot study that might affect its utility.

Question B. The Panel is asked to describe approaches for gathering additional data – e.g., data on the efficiency of transfer of surface residues to the skin surface (which has been identified as one of most critical model inputs based on the uncertainty analysis) – to improve the estimates of exposure and / or the level of confidence in such estimates, and with respect to these approaches, as well as the proposed pilot study, to comment on the cost of data generation, the amount of time to generate the data, and the degree to which the data will reduce uncertainty about the accuracy of the model estimates.

Issue 12. Prior to the availability of probabilistic models, such as SHEDS, OPP estimated the lifetime average daily dose (LADD) and corresponding cancer risk to pesticides via a deterministic approach using central tendency input parameters (median or mean values). Probabilistic models now allow OPP to express input parameters as distributions and subsequently generate a distribution of LADDs and corresponding pesticide cancer risks. In other words, the deterministic approach results in a single cancer risk value and the probabilistic approach results in a distribution of cancer risk values.

Question A. The Panel is requested to comment on whether in this probabilistic approach of using the upper bound arsenic cancer slope factor combined with using high-end LADDs would result in a significant overestimation of the risk for the more highly exposed percentiles of the population? If this is an overestimate, what other values would the panel recommended using as replacements, or in addition to the values that were used that would minimize the overestimation of risk without substantially underestimating the risk for such percentiles.

In this assessment, the estimated risks are considered approximations because inaccuracies may occur when exposures are summed across routes at the quartile level especially in the upper percentile. This is due to the way the Monte Carlo simulations were conducted and the outputs summarized.

Question B. The Panel is requested to comment on the range of percentiles, if any, at which there is a significant decrease in the reliability of the estimates of risk.

SUMMARY OF PANEL DISCUSSION AND RECOMMENDATIONS

Issue 1: Documentation, completeness, and clarity of the model source code and the exposure assessment report

The Panel concluded that the algorithms used in the model align with those identified in the exposure assessment report. The model was correctly programmed and the advice from previous FIFRA SAPs has been accurately incorporated and well documented. The exposure

assessment documentation is clear. The tables of user-specified assumptions are extensive but the assumptions hard-coded in the scripts could be highlighted better.

Issue 2. Modifications to SHEDS-Wood model code and the exposure scenarios selected

The general consensus of the Panel was that the current SHEDS-Wood model implementation represented a good faith effort on the part of the Agency. Even though one can question specific choices of distributional assumptions, overall the work seemed a reasonable effort and a sound basis for risk assessment within the limitations of available information.

It is clear to the Panel that the SHEDS-Wood model code is flexible enough to implement any reasonable new scenarios, given that distributions and associated parameter estimates of the random variable components of the scenario model can be specified. The Panel commented that anyone reviewing the current scenarios understands their limitations, including that the underlying population whose risk is being assessed is NOT children in general but is limited specifically to children contacting only CCA-treated public play sets. It was felt that this population limitation should be emphasized more in the documentation to avoid confusing the public. It is clear that this is not a population-based assessment for all children.

Issue 3. Key input variables and specification of associated variability distributions

It was the consensus of the Panel that, by and large, the best information on input variables at this time has been used. The communication of this information by the Agency could be better, however, since the process by which professional judgment is incorporated into the selection of data sets and distributions is not always clear. The impact of this lack of clarity is that the model appears less reasonable and scientifically sound than it probably is.

The Panel concluded that the set of variables related to human activity patterns (average number of days per year a child plays around CCA-treated playsets; frequency of hand washing; daily soils ingestion rate; average fraction of non-residential time a child plays on/around CCA-treated playsets) would benefit most from additional work by the Agency, and the impact of professional judgment more systematically addressed.

Issue 4: Methods and results for sensitivity and uncertainty analyses

The Panel found in general that the methods and results of the SHEDS-Wood model sensitivity and uncertainty analyses were approached in a useful and suitable manner. The conclusions of the sensitivity and uncertainty analyses are robust with respect to choice of analytical method. Nevertheless, the results of the variability and uncertainty analyses may be limited by the application of parametric statistical methods to probability distributions of model inputs and outputs that are highly skewed.

The bootstrap approach used to construct probability distributions representing uncertainty appeared to be implemented appropriately. Although alternative approaches are available for fitting uncertainty distributions from available data, using such methods is unlikely

to yield an appreciable difference in the uncertainty that can be extracted directly from a given data set.

In cases where the available data are applicable (i.e., specific to the model use) and representative (e.g., an appropriate sample of U.S. children), the uncertainty distributions described in the SHEDS-Wood report are probably reasonable and in general appear appropriate. In cases where the available data are not specific to their use in the model or representative of the appropriate portion of the U.S. population, then the uncertainty distributions generated by the bootstrap method may not be appropriate. Generally, it is likely that overall uncertainties are substantially understated because (1) influential variables for which no variability estimates were made were also not subject to the bootstrap uncertainty analysis, and (2) any procedure that relies on internal fluctuations within a data set will tend to incorporate only random error and neglect sources of systematic error among studies, such as unrepresentativeness of the studied population for the target population of exposed children.

Omitted from the uncertainty analysis is a lack of knowledge about the appropriate scenarios to include in the model and the algorithms (and corresponding data) used to simulate physical events. The Panel recommended that the Agency perform additional uncertainty analyses that include the parameters not treated as uncertain heretofore. In addition, the Agency should articulate the purpose of the uncertainty analysis is to aid in establishing a protocol for expressing uncertainty about the various model inputs.

Issue 5: Special Model Simulations

The Panel was generally satisfied that the special simulations conducted by the Agency are well justified. The scenarios investigated are logical additions to the overall sensitivity analysis and are in some cases directly responsive to stakeholder concerns.

Issue 6: Evaluation of the SHEDS-Wood model results

The Agency adequately documented six other exposure assessments in terms of the dose equations, input variables, and the levels of estimated exposure. In general, the exposures from these exposure assessments are in the same range as the output from the SHEDS-Wood model. In some cases, this may be due to overlap of the data available for the exposure assessments. The comparison revealed the limitations for comparison of these data sets due to their different approaches. The comparison neither validates nor invalidates the estimates from the SHEDS-Wood model.

Issue 7: Overall completeness and acceptability of the SHEDS-Wood probabilistic CCA exposure assessment

The Panel commended the Agency on an overall conscientious effort to respond to the various suggestions made by the previous FIFRA SAP. Overall the forms used by the Agency to describe the distributions are reasonable, and the Panel believed that other reasonable distributional forms are unlikely to appreciably alter the principal findings.

Issue 8. Formation of chemical complex after fixation

The Panel concluded that the Nico study, while important in the understanding of the nature of the Cr and As fixation in CCA wood and of the nature of the complex in wood particles, may not represent dislodgeable residues in general.

Issue 9. Relative Bioavailability (RBA) of dislodgeable wood residue

The Panel concluded that: (a) inadequacies in the study design; (b) the likelihood that actual residues found on skin are more bioavailable than in CCA wood residue samples; and (c) the likelihood that ingested CCA wood residue samples are more bioavailable in pigs than in humans, leads to conflicting possible interpretations of the Casteel et al. study. Thus, due to these deficiencies, the Panel could not suggest a value for the RBA of CCA-wood residues dislodged by skin.

Issue 10. Dermal absorption of dislodgeable wood residue

No quantitative estimate of dermal availability from CCA wood residue samples can be derived from the 2003 Wester et al. experiments. That study therefore represents insufficient grounds for alteration of the dermal bioavailability assumption used in SHEDS-Wood. The Panel noted that the current default dermal availability used by the Agency (a Beta distribution with mean and median of about 3% per 24 hours) falls closer to the low end of the 2-8% range of availability of inorganic arsenic that would be derived from the 1993 and 2003 Wester et al. studies if correction by intravenous response is assumed appropriate for dermal application of inorganic arsenic; that it is similar to an adjusted LOD for the CCA wood residue sample experiments, and that the form of arsenic transferred to the skin of persons contacting decks and playsets is unknown.

Issue 11. Proposed biomonitoring pilot study

The Panel concluded that the proposed biomonitoring study by the Wood Preservative Science Council, as it stands, is not responsive to the 2001 SAP request. It is more appropriately a "Preliminary Study" in which data of some potential utility may be gathered, but which in no way assesses exposures or doses likely to be experienced by the target group: children coming into contact with CCA-treated wood products. The study proposal as presented is deficient in many ways, some of which may be matters of the level of detail presented. The Panel questioned whether the preliminary study could be carried out successfully to address the goals mentioned.

It is the Panel's recommendation that a proposal for an appropriate pilot/preliminary study responsive to the recommendations of the 2001 SAP be discussed before implementation by all stakeholders– the public, EPA, and industry, and re-fashioned to be more responsive to all needs. After receiving input from these three groups, a new study design should, if appropriate, be amended so that it may be implemented in a way that provides information useful to all

parties and reflective of the need to understand exposure through this specific pathway.

The willingness of the regulated industry to entertain outside peer-review in this matter is encouraging as each stakeholder will be involved in various study components. With more thorough peer-review including involvement of EPA SHEDS-Wood personnel, a re-designed biomonitoring study could be an excellent source of information on actual levels of exposure and absorption, and be used to improve the SHEDS-Wood model.

Issue 12. Lifetime Average Daily Dose and Estimate of Risk

The Panel concluded that it is not appropriate to characterize the quoted arsenic cancer slope factor as an "upper bound." The arsenic cancer slope factor cited by the Agency is derived from a central estimate ED01. In the spirit of the extensive sensitivity analysis performed by the Agency on the exposure estimates, the Panel believed it would be fair and appropriate for the Agency to at least disclose the magnitude and direction of change in the CCA risk estimates that would result from adoption of the revised NRC estimates and other technical considerations that are under current discussion within the Agency on arsenic and other cancer risks.

PANEL DELIBERATIONS AND RESPONSE TO THE CHARGE

The specific issues to be addressed by the Panel are keyed to the Agency's background documents "A Probabilistic Exposure Assessment for Children Who Contact CCA-Treated Playsets and Decks Using the Stochastic Human Exposure and Dose Simulation Model for the Wood Preservative Exposure Scenario (SHEDS-Wood) – Draft Preliminary Report" and "A Probabilistic Risk Assessment for Children Who Contact CCA-Treated Playsets and Decks – Draft Preliminary Report", dated November 10, 2003, and are presented as follows:

Issue 1: Documentation, completeness, and clarity of the model source code and the exposure assessment report

Both the SHEDS-Wood source code and the probabilistic exposure assessment report have been significantly revised since the August 2002 SAP.

Question A: The Source Code Directory on the CD provided to the SAP includes 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 CCA exposure assessment report? Does the revised SHEDS-Wood version 2 code (i.e., the code submitted for the December 2003 SAP) accurately reflect changes to the version 1 methodology (i.e., the code and methodology presented to the August 2002 SAP) described in the report?

The Panel concluded that the algorithms used in the model align with those identified in the exposure assessment report. The model was correctly programmed and the advice from previous FIFRA SAPs has been accurately incorporated and well documented in the Agency's background document "A Probabilistic Exposure Assessment for Children Who Contact CCA-

Treated Playsets and Decks". The more important issues are the assumptions and design of the model and the data used to set up scenarios for the examples.

Much is gained by using SAS. The model is coded in relatively few lines and the speed and file handling capabilities of SAS are available. The model's code is simple, easily inspected and easily modified. Most of the assumptions are in separate tables, easily edited by the user, rather than hard coded. Most calculations are simple products of factors.

The scripts to produce graphical and tabular reports were not provided, so it was difficult for the Panel to interpret the trial runs. Thus, the Panel was not given enough information to permit a thorough code audit. A table is needed to define all the variables and cross-references linking the description of the algorithm to the various scripts. However, based on available information, the Panel determined that the code was acceptable.

The Panel raised a major concern that some assumptions that are hard-coded into the scripts are less likely to be questioned by users. In particular, the calculation of the height of a child who has no height from the previous year seems inconsistent in that one random monthly gain in height is generated and multiplied by the number of months of age. This makes for much greater variability in height compared to generating an independent increment for each month, as is done elsewhere in the model. Another inconsistency is that if the child is over age 6, the growth parameters for a child over age 6 are used for this one-month increment and applied to all prior months of life, including growth before age 6.

Another unusual feature is the way the last time period of the day is forced to have a contact event if there has to be one that day but it hasn't occurred earlier in the day. This may introduce a bias, which could be avoided by selecting all times of contact at once at the start of the day. Finally, the Panel concluded that it was not clear how many assumptions are actually hardcoded in the script or how important this may be to the overall performance of the model. Information was not provided on how weighted activity sampling was implemented in the code.

Question B: The SHEDS-Wood CCA exposure assessment report presents the model construct, selected model inputs, model results, and comparison to other CCA model estimates. Please comment on the clarity, completeness and usefulness of this document.

The exposure assessment documentation is clear. The tables of user-specified assumptions are extensive but the assumptions hard-coded in the scripts could be highlighted better.

The report assumes that a user interface will be available for setting up scenarios and analyzing results. Without that, SAS expertise is necessary if anyone is to use the model and the report alone does not provide enough documentation.

The comparisons with other CCA model estimates have to be done. However, one Panel member noted that there are so many user-specified assumptions in the model, one could probably adjust a few assumptions and make SHEDS-Wood agree with any other model.

However, even if such functions were performed, they wouldn't prove that either model was correct or gave correct predictions.

Issue 2. Modifications to SHEDS-Wood model code and the exposure scenarios selected a number of modifications to the model code and scenario-specific changes have been made to the SHEDS-Wood model since the August 2002 SAP.

Question A: Considering the limitations of available information and state-of-the-art modeling methods required for the assessment of children's exposures from contacting CCA treated wood residues and CCA containing soil, are the revisions made to the SHEDS-Wood code or algorithms scientifically sound and acceptable?

The general consensus of the Panel was that the current SHEDS-Wood model implementation represented a good faith effort on the part of the Agency. Even though one can question specific choices of distributional assumptions, overall the work seemed a reasonable effort and a sound basis for risk assessment within the limitations of available information.

While the SAP was asked to discuss the scientific soundness of the code and algorithms, the scientific soundness has not been defined. For discussion purposes, scientific soundness as it relates to the SHEDS-Wood code and algorithms must: 1) express the logic of the micro-simulation model proposed for exposure; 2) be transparent enough that it can be repeatable by other researchers wishing to replicate this model, possibly in another format; and 3) be based on generally accepted data, processes and parameters.

The SHEDS-Wood code does faithfully express the underlying micro-simulation model it was designed to mimic. There are components of the micro-simulation model that are contentious and some components will change or be added in the future. The structure of SHEDS-Wood is of sufficient flexibility to facilitate those changes and additions. The speed with which the SHEDS-Wood team was able to implement the many changes proposed by the August 2002 SAP demonstrates this point.

SHEDS-Wood is implemented in SAS and for the most part is transparent to anyone familiar with SAS scripts. This is a point in its favor but also a detriment. The user must have SAS to be able to run the simulation. SAS provides a flexible environment for model modifications and enhancements. The development in SAS represents a compromise between: 1) flexibility in model implementation; 2) time available to develop the model; 3) providing a model that is transparent; and 4) model usability.

Actually the version of SHEDS-Woods presented to this Panel is more transparent than the previous version because most of the complex up-front menu structure is gone and the user needs only modify a macro cell or a couple of datasets to change the model run. Because of this, the Panel concluded that the SHEDS-Wood model is sufficiently transparent as to be repeatable. However, this is not to imply that it would be a simple matter to repeat this structure in another programming environment. The simulation of temporal activity patterns implemented in the code is quite complex and is not something that could easily be implemented, as for

example in a spreadsheet environment. Just because the SAS code can be followed does not mean that this implementation is simple.

Industry representatives were able to follow the model sufficiently both to understand its operation and provide a critical evaluation. These external reviewers were also able to suggest how the micro-simulation model should be changed and the Agency was able to quickly implement these changes and assess the impact of these changes on the final estimated exposure distribution. Other proposed changes, e.g., indoor versus outdoor hand-to-mouth contact component distributions or intensity of contact modifications or even adding an unloading process as suggested in the industry comments, or other behavior changes as suggested in the public comments could also be implemented and evaluated—quickly and responsively.

An important issue is the use of generally accepted data, processes and parameters. This is where the "limitations of available information" clause of the question comes into play. In implementing the micro-simulation model, the developers have had to use best professional judgment in choosing which processes (e.g. routes of exposure) to be included and which to exclude. They have referenced the literature and engaged researchers to get the best data, but in some cases the data are inadequate or unavailable and hence best professional judgment must be invoked again. Finally, because this is a probabilistic risk assessment, many of the model components have been conceptualized as random variables and as such distributions for these random variables must be specified. This is a relatively easy task when supporting data are available and a daunting task when little or no data are available. There are in this SHEDS-Wood implementation a number of components whose distributions are based more on professional judgment than on data. Use of professional judgment is unavoidable in as ambitious an undertaking as this.

One Panel member noted some of the code changes are related to the development of probabilities for switching among high, medium and low activity levels and that these seem wholly based on California data. In addition, the information in the Consolidated Human Activity Database (CHAD) on playset use also comes almost entirely from a small dataset from California. The dependency of these key model components on information from a limited geographical location and small sample size could have large impacts on the simulation results for other populations. Similar questions were posed regarding the SHEDS-Wood approach to bathing events. It is not clear from the documentation that what is implemented in the model coincides with the available data (Freeman et al., 2001).

As was mentioned in the public comments, scientific inquiry produces insight through the examination of competing models. When choosing among competing simple models, the use of a validation dataset is critical to determining the best among candidates. As the model under consideration gets more complicated, even something as simple as a multiple linear regression, the number of possible competing models can be large and the choice of the best model using a validation dataset increases proportionally in difficulty. In addition, as the model gets more complex, our ability to fully validate the model decreases. Validation of a complex model actually involves what the Agency has attempted and what has been suggested by previous FIFRA SAPs, examining each model component, determining the validity of the parts and how

logically the components are put together. This should include looking at distributions of intermediate results (e.g. total annual time in contact with playsets) and comparing them to deterministic median values when available or with expert-opinion on reasonable estimates. The SHEDS-Wood model developers should consider developing one or two experiments that challenge the model. Many of the studies proposed by the CCA industry appear focused in that direction.

Question B: The SHEDS-Wood model has been modified using feedback from the August 2002 SAP. In particular, the recent assessment, includes: assessment of exposures of children contacting only CCA treated public playsets; sensitivity of results to changing the age group of exposed children to 1-13 years, and; a separate analysis for children exhibiting pica soil ingestion behavior. The Panel is requested to comment on the appropriateness of the new exposure scenarios in the revised probabilistic exposure and dose assessment.

It is clear to the Panel that the SHEDS-Wood model code is flexible enough to implement any reasonable new scenarios, given that distributions and associated parameter estimates of the random variable components of the scenario model can be specified. The Panel's comments focused primarily on ensuring that anyone reviewing the current scenarios understands their limitations. These limitations seem to be:

1) That the underlying population whose risk is being assessed is NOT children in general but is limited specifically to children contacting only CCA-treated public play sets. It was felt that this population limitation should be emphasized more in the documentation to avoid confusing the public. It is clear that this is not a population-based assessment for all children.

2) The handling of exposure for 7-13 year olds in the 1-13 year old assessment needs further clarification. The approach to extending the model from 1-6 to 7-13 years was an attempt of assigning to 7-13 year olds 25, 50, 75, or 100 percent of what was calculated for the 1-6 year olds. The Panel noted that since it is assumed that cancer risk is proportional to lifetime exposure, setting the exposure of older children in terms of a percentage of the exposure of younger age children, allows one to question the impact of exposure in older children. Other scenarios, such as not zeroing out exposures beyond age 13 are not examined. No guidance is offered as to the most supportable scenario. The assessment does not discuss the sensitivity of model outputs to changes in exposure levels in 7-13 year olds. Finally, it does not seem that the 7-13 years olds scenarios take into account even the limited information available in CHAD for children in this age range.

Some Panel members believed that the serious data limitations for the 7-13 year olds suggest that it may be best not to include scenarios that address exposure for this age group. Without new information on mouthing behavior for the 7-13 year olds, an assessment for this age group has little basis in reality. Other SAP members indicated that the 1-13 years scenarios do provide risk assessors useful information at little extra expense; an improvement over not doing the scenario at all. It was felt that while mouthing behavior for 7-13 year olds should decrease with each year of age, other activities, such as eating food in the play area may

increase, resulting in increased exposure. The Panel recognized that on this topic there is the need to balance the cost of additional information with the expected benefit in improved exposure scenarios. The Panel asked that the SHEDS-Wood developers identify what information is available for this older age group and attempt to limit the scenarios to the more supportable bounding conditions.

3) Recent information on children exhibiting high soil consumption levels suggest that these children might not be eating the type of material found around playscapes in playgrounds, i.e. sand, ground-up rubber, rubber matting, pea gravel, or wood chips (NPPS, ASTM F-1292-99). True soil pica behavior is typically assumed to be associated with children attempting to alleviate a nutrient deficiency through consumption of soils or clays. While the pica scenario presented is useful for assessing extreme soil consumption, it may not be that useful as a surrogate for children who do excessive mouthing related to the transfer of residues from surfaces (for example, children with autism). One Panel member indicated that new activity information on autistic children is expected soon and that these data may provide the foundation for a new pica scenario.

Mouthing of playsets or decks which may contain As residues and leachate was not evaluated in the EPA pica model. Thus, the Panel suggested that the Agency consider children's ingestion of non soil items in their exposure assessment.

Issue 3. Key input variables and specification of associated variability distributions

Sensitivity and uncertainty analyses of the SHEDS-Wood model results identified the following as key input variables influencing the model results: wood surface residue-to-skin transfer efficiency; wood surface residue levels; fraction of hand surface area mouthed per mouthing event; and GI absorption fraction for residues. In addition to the above variables, sensitivity and uncertainty analyses also indicated the importance of following additional variables: average number of days per year a child plays around CCA-treated playsets, frequency of hand washing, daily soil ingestion rate, and average fraction of non-residential time a child plays on/around CCA-treated playsets.

Question A. Has the Agency used the best available information for developing input distributions for these variables? If not, are there any other data that EPA should be aware of? Considering the limitations and uncertainties with available information, are the choices made in developing distributions for each of these key variables using the available information reasonable and scientifically sound?

It was the consensus of the Panel that, by and large, the best information on input variables at this time has been used. The communication of this information by the Agency could be better, however, since the process by which professional judgment is incorporated into the selection of data sets and distributions is not always clear. The impact of this lack of clarity is that the model appears less reasonable and scientifically sound than it probably is.

While in most cases it appears that the Agency used the best available data,

documentation in some places is difficult to follow or review because some papers are in press or are reports that have not passed peer review. What is less clear is the documentation of the role of professional judgment in choosing one study versus another deemed of lesser quality or relevance. Some of these are better documented than others, such as the CPSC, ACC and EWG data on residues on the hand, residues on surfaces, and soil concentrations detailed in Table 8 of the Agency's background document "A Probabilistic Exposure Assessment for Children Who Contact CCA-Treated Playsets and Decks".

The Panel noted that new data should be incorporated into the model as it becomes available, especially in cases where the initial model variables were uncertain and/or largely developed using professional judgment. The only data set that the Panel identified that may be helpful but which was not incorporated into the SHED model are some children's activity data from the Minnesota Children's Pesticide Exposure Study (MNCPES). MNCPES collected week-long time-activity data from 102 children, ages 3-12 and 6-7 documenting the time soil or dirt was in contact with the skin, showering/bathing frequency, and the number of times a child washed his/her hands. These data should be reviewed carefully as it represents a mixture of child and adult caretaker responses. The Panel noted that EPA ORD already has these raw data in their possession. The Panel suggested that for prioritizing model improvement activities, a table listing the variables in which professional judgment has the biggest impact be listed in rank order.

Question B. In some of these instances (see Table 12, page 58), because of data limitations, the Agency has made simplifying assumptions to represent them as point estimates based on professional judgement. Are the simplifying assumptions presented in the draft exposure assessment for making these decisions adequately supported by relevant scientific data? Are the choices made to quantify these variables (i.e., selected distributions or point estimates) reasonable and sound?

The Panel reviewed two sets of key variables: those related to residue ingestion (wood surface residue to skin transfer efficiency; wood surface residue levels; fraction of hand surface area mouthed per mouthing event; gastrointestinal absorption fraction for residues) and those related to human activity patterns (average number of days per year a child plays around CCA-treated playsets; frequency of hand washing; daily soil ingestion rate; average fraction of non-residential time a child plays on/around CCA-treated playsets). It was the view of the Panel that the second set of variables related to human behavior would benefit most from additional work by the Agency. The impact of professional judgment in choosing model input values also needs to be more systematically addressed.

Table 12 of the Agency's background document "A Probabilistic Exposure Assessment for Children Who Contact CCA-Treated Playsets and Decks" lists 41 total variables, some of which are chemical specific. The Panel noted that the use of the term "point estimate" is confusing in the context of the table because the "point estimate" implies a single data point that is the same for all simulation runs, where (as the Panel learned through presentations at the FIFRA SAP meeting) this is not exactly what was meant by EPA scientists and thus needs some clarification. This is especially important in cases where the specific probability reported is

derived from professional judgment. The Panel noted that it would be useful to add a column indicating which variables were part of the formal uncertainty analysis and which were uncertain but not included in the formal uncertainty analysis. This is necessary because there are really two types of uncertain variables in the model: those that have too few data to make a distribution and thus are point estimates, and those with uncertain distributions. The document does not make it clear how these are different and why they should not both be part of the formal uncertainty analysis process in SHEDS-Wood.

The following sections summarize the Panel's view on the specific variables listed above. The Panel noted that there are several other key variables that are not mentioned because they were applied as point estimates and therefore had no variability distributions or because they were not included in the sensitivity analyses. The Panel noted that Table 12 refers, implicitly and explicitly, to the Appendices at the end of the Agency's background document "A Probabilistic Exposure Assessment for Children Who Contact CCA-Treated Playsets and Decks". It would be helpful if the Agency referred to the goodness-of-fit tests and the figures in the Appendix more directly in Table 12. In addition, many of the figures should be properly labeled with units, page numbers, and descriptive titles that make clear the relationship between data and the variables/distributions used in the model.

Wood surface residue-to-skin transfer efficiency ($TE_{surf\text{-}skin}$**)**

The description of $TE_{surf\text{-}skin}$ as described on Table 12 and pages 69 and 70 of the Agency's background document "A Probabilistic Exposure Assessment for Children Who Contact CCA-Treated Playsets and Decks" appears reasonable. The Agency should better explain how the CPSC and ACC data were combined for the cold climate scenario. One Panel member noted that the median and geometric standard deviation were greater for the cold climate compared to the warm climate scenario and questioned whether this was due to combining data from the two sources.

Wood surface residue levels ($SR_{res,playset}$ and $SR_{res,deck}$**)**

The description of $SR_{res,playset}$ and $SR_{res,deck}$ as described in Table 12 and page 69 of the Agency's report appears reasonable. Again, it is not clear, however, how the CPSC and ACC data were combined for the cold climate scenario for arsenic. The Agency should clearly explain how the two data sets were combined. The Agency should also provide a rationale for using deck data for playsets.

From examining the information on wood surface residue distribution in Table 10 of the Agency's Background Document "A Probabilistic Exposure Assessment for Children Who Contact CCA-Treated Playsets and Decks", it became apparent to one Panel member that the reported minimum and maximum values were not symmetric (on the log scale) about the reported median. This led to a concern that the fitted lognormal distribution might not be fully accurate in describing the distribution of the underlying data. On request, Agency scientists supplied the underlying data from the ACC study for independent analysis by the Panel at the meeting. The Panel's analysis of these data is described below.

A first step was to examine summary statistics for the $\log_{10}$-transformed data (Table 1 below), and assess whether there was any reason to suspect systematic patterns of residue differences by age of the deck, or other reported characteristics. Briefly, it was apparent that freshly treated wood tended to have higher surface residue concentrations than weathered wood, but there was no clear and consistent tendency for the observations for decks exposed to the elements for many years to have systematically different geometric mean or standard deviations for concentration than decks exposed for shorter periods. The overall summary statistics for the warm climate data match the Agency's reported geometric mean and standard deviation. The Agency's summary analysis for cold climate states indicates slightly different summary statistics apparently because the Agency included CPSC data in the distribution reported in the document. Because the Panel was interested in examining potential heterogeneity in the data, it was decided not to mix in the CPSC observations for this purpose.

Figure 1 below shows lognormal probability plots of the overall ACC data for "warm" vs. "cold" climate states. Figure 2 below shows a similar plot separating data for Florida vs. Georgia (the two states represented in the "warm" climate category). The correspondence of points to the straight regression line in the log probability plots in Figures 1 and 2 are a quick qualitative indicator of how well an assumed lognormal distribution describes the data. Probability plots are plots of observed values of a variable (or the logarithm or other transformation of the values) versus a "z-score". The z-score is the number of standard deviations from the mean of a normal distribution that would correspond to a specific percentile of the cumulative distribution of the values. It can be calculated in Excel® using the "normsinv" function applied to a "percentage score" calculated from the cumulative ordinal distribution ranks using the formula $(I - 3/8)/(N+1/4)$ (Cunnane 1978) where I is the rank of a particular value in the ordered distribution of values, and N is the total number of values.

Table 1. Summary Statistics for the ACC Wet Deck Wipe Data

State	Deck Age (yrs)	Mean Log(deck wipe µg/cm^2)	Std Dev Log(deck wipe µg/cm^2)	N	Std Error Log(deck wipe µg/cm^2)	Geometric Mean	Geometric Standard Deviation
FL	Untreated	-1.749	0.284	20	0.0634	0.018	1.922
FL	0	-0.353	0.308	60	0.0398	0.443	2.033
FL	1 to 1.3	-0.633	0.445	150	0.0363	0.233	2.786
FL	5 to 6	-0.453	0.275	59	0.0358	0.353	1.885
FL	15	-0.708	0.261	91	0.0274	0.196	1.824
All Fl 1+ yrs	1 to 15	-0.620	0.377	300	0.0217	0.240	2.380
NC	Untreated	-1.774	0.280	20	0.0626	0.017	1.904
GA	Untreated	-1.837	0.201	16	0.0503	0.015	1.590
GA	0	-0.492	0.066	12	0.0192	0.322	1.165
GA	1 to 1.5	-0.771	0.170	58	0.0223	0.169	1.478
GA	4	-0.586	0.246	20	0.0551	0.259	1.764
All GA 1+ yrs	1-4.	-0.724	0.207	78	0.0234	0.189	1.611
All GA+FL **("Warm")**	**1 to 15**	**-0.642**	**0.351**	**378**	**0.0180**	**0.228**	**2.242**
PA	0	0.358	0.516	60	0.0666	2.282	3.278
PA	0.6 to 1	-0.585	0.207	150	0.0169	0.260	1.610
PA	5 to 8	-0.532	0.267	90	0.0281	0.294	1.849
PA	15 to 23	-0.542	0.260	108	0.0250	0.287	1.820
All PA ("Cold')	**.6 to 23**	**-0.558**	**0.241**	**348**	**0.0129**	**0.277**	**1.742**
All freshly treated	0	-0.042	0.547	132	0.0476	0.907	3.523

Figure 1.

Lognormal Probability Plots of Wipe Surface Concentration Distributions
for Aged (.6-23 Years) Decks in Warm Vs Cold Climates

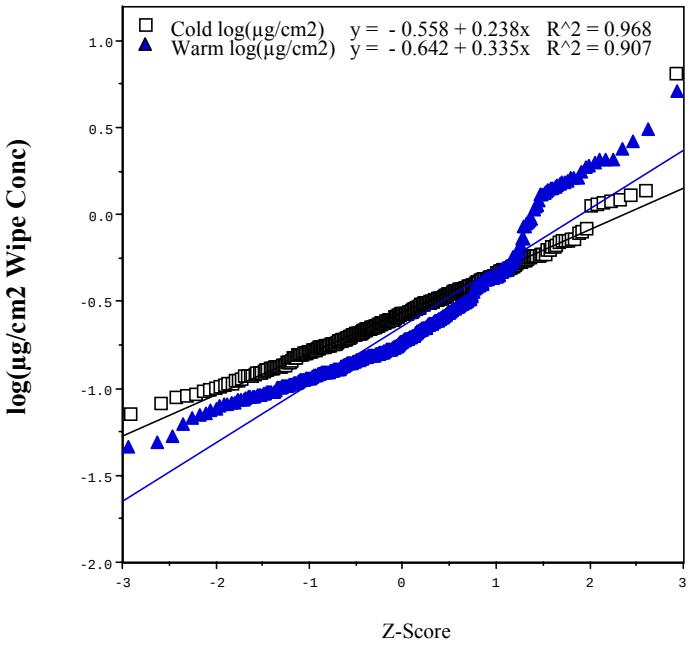
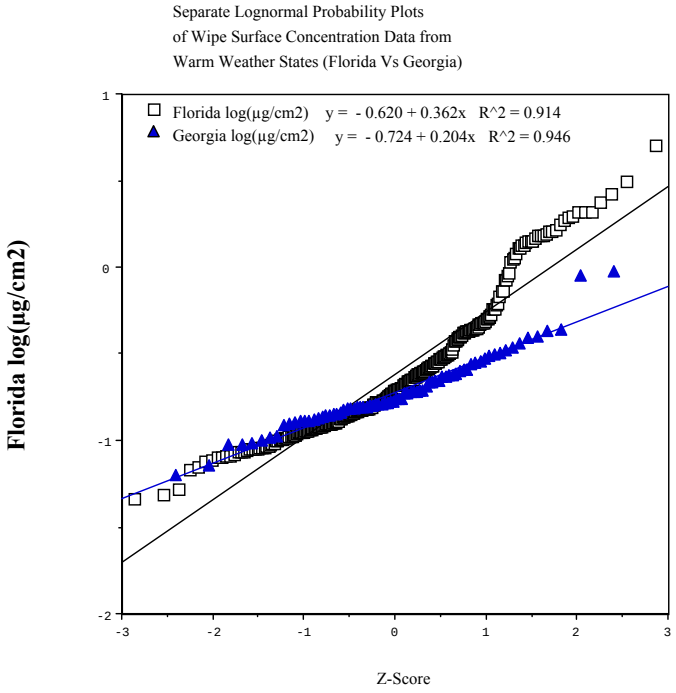


Figure 2.



As shown in Figure 1, the data points for the warm climate data in particular depart conspicuously and systematically from the straight line, corresponding to the fitted lognormal distribution. Both warm and cold climate data sets, however, show a similar pattern of departures, strengthening the conclusion that some improvement in the distributional description of these data is likely to be possible. The departures of the data from the lognormal are in a pattern that suggests that a mixture of two lognormal distributions might well better correspond to the underlying data with the distribution containing the smaller number of decks centered at a much higher level than the bulk of the decks. Mechanistically, a mixture of two lognormals might be produced if there were two populations of decks (or portions of decks) that differed appreciably in arsenic mobilization (perhaps because of differences in microbial activity or some differences in the chemical fixation of the arsenic in the original treatment).

To see how much a better distributional description for this parameter might alter the overall results of the SHEDS-Wood model, a comparison was made of the arithmetic mean observed in the underlying data with the mean predicted from the fitted lognormal distribution parameters (Table 2). It can be seen that the basic observations have means that exceed the means implied by the fitted lognormal distributions by about 12% and 4% for the warm and cold climate data sets, respectively. These calculations do not, therefore, indicate that there would be substantial differences in indicated population aggregate dosage. The differences might be more appreciable, however, for higher percentiles of the SHEDS-Wood modeled exposure distributions.

One final observation that emerged from examining the data is shown in Table 3 below.

The 700-odd data points in the ACC study come from only 25 different decks. This raises the issue of whether the modelers should really partition the overall cold and warm climate variances into within-deck versus between-deck components. A child might well visit the same deck consistently, but he or she would be unlikely to consistently come into contact with the exact same location on the deck.

Therefore while it might be appropriate to construct the distribution of exposures so that if only one draw from an among-deck mean residue distribution is used for a whole year of exposure, it is likely that the different contact events for each child would reflect the likely distribution of residue levels within individual decks. For long term exposure calculations, therefore, it might be appropriate to calculate each child's exposures from the distribution of arithmetic mean residue levels observed for the 25 decks (separated into the two cold versus warm subsets as before). This would of course reduce the N's to 12 and 13 for the two climate groups, and would likely reduce the estimated variability of this input among children (because the distribution of deck mean levels will have a smaller variance than the distribution of the raw observations). However this might more faithfully reflect the likely distribution of the arsenic residue concentrations that give rise to actual children's exposures.

Fraction of hand surface area mouthed per mouthing event

The Agency provided no rationale for choosing the beta distribution for fraction of hand surface area mouthed per mouthing event. In the Excel® spreadsheet provided on the website for Leckie et al. (2000), data are provided on only 3 children (although on page 20 of the Agency's background document "A Probabilistic Exposure Assessment for Children Who Contact CCA-Treated Playsets and Decks" 20 children are mentioned). The Agency should show how the beta distribution was derived from the data and refer the reader to the graphical and statistical justification of the choice of this distribution.

Furthermore, page 73 of the Agency's background document "A Probabilistic Exposure Assessment for Children Who Contact CCA-Treated Playsets and Decks" reports a 3-5 year old hand surface area as 200 cm^2. It is unclear if this is for both hands, palmar surface only, or all skin surfaces. The ACC-RTI study reports adult hand surface areas are between 107 and 188 cm^2. 200 cm^2 for hand size of 3-5 year old children is probably accurate for total skin surface of both hands for 2 year olds, but would underestimate 4 or 5 year old children. Palmar surface of a single hand (including fingers) for 3 year old children is about 55 cm^2, while for 4 year old children the palmer surface area is approximately 62 cm^2.

Table 4 below shows hand surface area data by age groups from two studies, the Children's Dietary Lead Study (CDLS) and the Rio Bravo pesticide exposure study (Black et al., submitted; Black et al., in prep.; Freeman et al., 2001; Shalat et al., 2003).

Table 2. Comparison of the Arithmetic Mean of the Raw ACC Surface Residue Observations with the Means Predicted from Fitted Unimodal Lognormal Distributions

Data Set	Arithmetic	Std. Dev.	Std. Error	Arithmetic	Obs/Predicte

	Mean of Data			Mean Predicted from Fitted Lognormal	d Arithmetic Mean
Warm ACC	0.353	0.499	0.026	0.316	1.12
Cold ACC	0.336	0.389	0.021	0.323	1.14

Table 3. Decks Sampled for Each State in the ACC Observations

State	Decks	Total Number
Florida	**T,Y,Z,AA,AB,V,W,AC,S,U**	**10**
Georgia	**G,E,D**	**3**
Pennsylvania	**P,Q,R,M,X,L,I,H,N,K,O,J**	**12**
Total Decks		**25**

Table 4: Data on single hand palmar surface areas including fingers (cm^2) gathered from 2 studies

Age (months)	n	Mean +/- SD (cm^2)	Median (range) (cm^2)
Study: $CDLS_1$			
13-24	**16**	**51.6 +/- 6.5**	**52.2 (39.0-62.5)**
25-36	**36**	**58.8 +/- 6.4**	**57.7 (46.7-81.1)**
37-48	**13**	**58.6 +/- 4.6**	**58.9 (52.7-67.3)**
49-60	**2**	**63.7 +/- 2.2**	**63.7 (62.1-65.2)**
Study: RB_2			
13-24	**49**	**44.0 +/-5.3**	**44.0 (31.0-55.5)**
25-36	**52**	**51.9 +/-6.6**	**52.0 (34.5-66.0)**
37-48	**34**	**54.5 +/- 5.2**	**53.5 (41.5-69.5)**
49-60	**15**	**61.9 +/- 9.4**	**61.5 (49.0-88.0)**

1. CDLS - children's dietary lead study (ethnically heterogeneous population)
2. RB - Rio Bravo pesticide exposure study (ethnically homogeneous population)

These surface areas can be used to test the accuracy of the hand areas used in SHEDS-wood, which were derived from height-weight ratios. The hand palmar surface is reported as 25% of the entire hand surface and each finger is presented as 10% of the hand. If we take a hand area of 200 cm^2 and assume that each finger is 10% of the hand, then placing 3 fingers in the mouth would account for 60 cm^2 of surface mouthed, not 20 cm^2 as reported in the document. If one assumes that only half of each of the three fingers is mouthed, the mouthed surface area

for the 3 fingers is still greater than the estimates provided in the Agency's document.

Assuming that each finger is 10% of the hand is a rough generalization, it is probably acceptable at this level of assessment, but does not accurately reflect either the proportions of the various fingers or the change in palm/finger ratio that occurs with age.

Related to this issue is how mouthing behavior data is incorporated into the model. The larger issue that was not addressed in the question to the Panel but should be examined more closely is the issue of dermal loading over time.

SHEDS-Wood uses the distribution of all mouthing behaviors rather than the distribution of mouthing behaviors linked to subsequent behaviors. The overall distribution of mouthing events is driven by indoor mouthing, which is not representative of less frequent mouthing activities outdoors. The SHEDS-Wood scenario ingestion is modeled as a more or less direct occurrence after playset contact. There are minutes to hours of other contacts both indoors and outdoors before removal by mouthing or hand washing occurs. The work of Rodes (2001) and Geno et al. (1996) suggest that there is a maximum amount of material (particles) that will adhere to hands and that over a period of time there will be loading, dislodging from the skin, and reloading. If this is the case, then the materials that adhered to the hands at various outdoor play locations may not be the materials that are on the hands when the child enters the house because of the range of post-CCA-treated playset contact activities outdoors, and there are likely additional contacts with surfaces and objects indoors prior to mouthing or hand washing. Given this scenario, it is very likely that the materials that the child mouths indoors or that are removed by hand washing are not the materials that adhered to the hand on the playset. This is a scenario that could be tested with structured laboratory experiments.

Below in Table 5 are summary data on the proportion of mouthing that occurs outdoors from several observational studies for children who spent time both indoors and outdoors. Percent mouthing is driven by the greater amount of time children spend indoors compared to outdoors as well as the difference in mouthing rates (freq/hr) that occurs indoors and outdoors. Some of the highest percent values were from children who exhibited infrequent mouthing behaviors anywhere so that a modest change in frequency can produce a large effect when the data are presented in this fashion.

Table 5. Fraction of Mouthing Events Outdoors (median and range) for Children Observed Both Indoors and Outdoors

Location	Population	N (# of children)	% of mouthing occurring outdoors Median (range)
Minnesota[a]			
	3-5 year olds	3	3 (0-54)

	6-12 year olds	14	0 (0-91)
New Jersey[b]			
	3-5 year olds	18	0 (0-45)
Texas[c]			
	< 3 years old	50	10 (0-91)
	3-5 year olds	23	11 (0-86)

a. Freeman et al., 2001
b. Freeman et al., 2004; Hore et al., submitted; Reed 1998, thesis; Hore 2003, thesis
c. Black et al., submitted; Black et al., in prep

GI absorption fraction for residues

For arsenic, the Agency's background document "A Probabilistic Exposure Assessment for Children Who Contact CCA-Treated Playsets and Decks" should refer the reader to the Appendix with the goodness-of-fit figures for the ACC 2003 data showing how well the beta distribution fit the underlying data. For chromium, the new Nico et al. (2003) data suggests that 100% absorption is likely an overestimate. The Panel's review of the Nico et al. study is provided in response to Issue 8.

Average number of days/year a child plays around CCA-treated playsets

The input variable "average number of days/year with public playset contacts" is a fixed user-defined variable. The Agency has not adequately described the rationale for choosing the warm and cold climate estimates of 126 days and 54 days, respectively. In addition, it would seem that this variable would change with age and there is no rationale for public and private playset play to be the same. There are simply too many assumptions made in the second and third paragraphs of page 66 of the Agency's background document "A Probabilistic Exposure Assessment for Children Who Contact CCA-Treated Playsets and Decks" to determine if a single value is reasonable. A clearer description of the days/year will help to answer many of the questions of the Panel.

Frequency of hand washing

Reported hand washing frequency, which is usually stated as events per day, is often obtained from parental reports that should be viewed critically. One Panel member noted that nearly all parents will say that children wash their hands 3-5 times a day. Given existing data on day long video observations of children, the Panel judged this a likely over-estimate of hand washing frequency.

The Agency should provide these data from the various studies and show how it was combined to determine the lognormal distribution for the hand washing events/day. In addition, it would seem that hand washing is a discrete variable and should not be represented by a lognormal distribution. The Agency should explain how these data were used in the model.

Mean hand washing removal efficiency is reported as 0.593, interquartile range 0.548-0.638 (p.62 of the Agency's background document "A Probabilistic Exposure Assessment for Children Who Contact CCA-Treated Playsets and Decks"), while hand to mouth dermal transfer fraction (based on OP studies rather than metals) is reported as 0.780, interquartile range 0.721–0.849 (p. 63). While the Panel is aware of no data to counter these values, it seems unlikely that hand washing would be less efficient than dislodging via mouth contact, unless one assumes that mouthing events are active and involves prolonged sucking/licking of the fingers, which is not mentioned in the supporting text. Much of the mouthing data that is reported in the literature are light, incidental behaviors as opposed to serious sucking/licking.

Daily soil ingestion rate

The derivation of this distribution appears reasonable. However, the Agency should explain more clearly that if an ingestion rate of > 500 mg/day arises, the children were removed from the analysis and placed in the pica analysis, if that is in fact the case.

Average fraction of non-residential time a child plays on/around CCA-treated playsets

The macroactivities reported in CHAD are "not sufficient" to define contact specifically with CCA-treated wood, or even time spent on playsets of any kind. The Agency's choice of several of the "Suitable CHAD locations for public (non-home) playset contact" appears to have little to do with potential playset contact and should be removed from consideration or much better explained since this category includes sidewalk/street/neighborhood, within 10 yards of street, amusement park, park/golf course, etc. The Agency's background document "A Probabilistic Exposure Assessment for Children Who Contact CCA-Treated Playsets and Decks" is not very clear on how these numbers are justified through later data manipulations.

Other Issues

One Panel member suggested that since parameters having key impact have been identified, the model run can be simplified by using point values instead of a distribution for those parameters with no significant impact on the overall model output, and especially data of lesser quality or with no assurance that it is representative for the scenario in question. It was also noted that within the results presented in the Agency's background document "A Probabilistic Exposure Assessment for Children Who Contact CCA-Treated Playsets and Decks", the playset arsenic exposure component appeared to stay the same with or without deck exposure, and for residential or public playsets. This may indicate that the scenario subset need not be separately modeled. Some of the advantages of holding down model complexity are: ease of presentation and general understanding of the model, ease of spotting errors, and balancing the workload associated with complexity with value-added for risk managers.

Question C. Are the methods used for fitting variability distributions that are assigned to model input variables for the CCA assessment appropriate?

This question referred to two issues: 1) the use of professional judgment is a major part

of choosing data for fitting distributions, and 2) the statistical process used to fit distributions. In an ideal world the first process informs the second. The Agency's background document "A Probabilistic Exposure Assessment for Children Who Contact CCA-Treated Playsets and Decks" should also more clearly identify the distributions that were constructed primarily on the basis of professional judgment. This would help in assessing the uncertainty in the overall model, and assist in making clear the difference between uncertainty due to the lack of data as opposed to the uncertainty associated with parameterization of the proposed model.

One concern about the input data is their representativeness and consistency. When more than one source of data are combined for a variable distribution, the evaluation of their compatibility should be more clearly documented. The Panel noted that there were apparent inconsistencies in the data used for similar variables, most likely due to their different sources. For example, there was a directional change between the warm and cold climate for arsenic soil concentration near the playset and near the deck. This either should be corrected or the reasons for the inconsistency documented.

The Agency's background document "A Probabilistic Exposure Assessment for Children Who Contact CCA-Treated Playsets and Decks" described how data were used but not necessarily how the variability distributions were fit to raw data. It appears that the Agency had used maximum likelihood and method of moments methods to fit the distributions. The Panel noted that to successfully use maximum likelihood methods, the Agency must have sufficient data, which is not always available. The Agency could also use indices like the Akaike Information Criteria (AIC) index to justify distribution choices. The method of moments is much less rigorous than the maximum likelihood methods. Sometimes the estimates obtained directly by linking data moment to theoretical moment is appropriate, but for some distributions this is not a useful approach. One does not know what happens when you match the moments of a triangle distribution to that of a beta, as the Agency seems to have done in a number of cases. In general the Panel believed that it would be better to incorporate plots of the beta and triangle fitted distributions so individuals can tell for themselves if they appear to be correct.

In the case of a number of variables described on pages 65-76 of the Agency's background document "A Probabilistic Exposure Assessment for Children Who Contact CCA-Treated Playsets and Decks", the Agency says for example "We fit a triangular distribution with minimum 0.25, mode 0.5, maximum 0.75, then fit to the triangular distribution a beta distribution with bounds at 0 and 1 and parameters 12.35 and 12.12…" without specifying how this was done. In such a presentation, it appears fitting was done via a method of moments, but it is difficult to tell if a Beta (12.35, 12.12) fits this triangular distribution well.

Fitting appears to be problematic especially in cases where more than one study is available to estimate variability in particular lognormally distributed parameters (e.g., the daily soil ingestion rate, page 72 of the Agency's background document "A Probabilistic Exposure Assessment for Children Who Contact CCA-Treated Playsets and Decks"). In this case the SHEDS-Wood group has taken an arithmetic average of geometric standard deviations. In another case (the soil-skin adherence factor, pages 72-73 of the Agency's background document "A Probabilistic Exposure Assessment for Children Who Contact CCA-Treated Playsets and

Decks."), they chose to compute a simple average of variances. The Panel suggested that within-study variances should generally be combined by computing weighted averages. For example, if M and N are the number of individuals for whom measurements are available, resulting in estimated geometric standard deviations of S and T (each calculated as the antilog of a conventional standard deviation of the log-transformed values), then a combined geometric standard deviation should be calculated as:

$$(\{(M-1)*[\log(S)]^2+(N-1)*[\log(T)]^2\}/\{M+N-2\})^{0.5}$$

Some Panel members had general reservations about the foundational triangle methodology. It seems likely to be inferior to directly fitting the desired distributional forms to either the raw data or summary data (e.g. mean, standard deviation). However this is not likely to have made a substantial difference in the overall results. The difference could be addressed with the aid of a limited number of case studies comparing a properly direct-fit distribution with the distribution derived from the foundational triangle approach.

Question D. The Panel is requested to comment on whether any other model inputs are either key drivers of results or sources of large model uncertainty. Do these model input variables and the distributions assigned to them appropriately reflect available scientific data? Did EPA appropriately integrate the available data to derive the distributions for these input variables?

With the exceptions noted above, in general the Panel concluded that the Agency appropriately integrated available data and derived appropriate distributions. As a general approach the Panel concluded that it was important to devote time to fixing the variables that had "credibility problems," i.e., those that were largely constructed via the undocumented process of professional judgment and were the subject of much public comment. Effort should be spent improving the clarity of the presentation so that the major determinants of these variables are well understood. Doing so will also help the Agency and stakeholders obtain crucial data to improve these variables. For example, it was the view of many Panel members that there were large uncertainties in the use of CHAD diaries and how the CHAD diaries were applied. It would seem as though the outcomes could be validated with a relatively simple telephone survey.

Issue 4: Methods and results for sensitivity and uncertainty analyses

EPA's draft CCA Exposure Assessment includes a formal sensitivity and uncertainty analysis as well as discussion of various sources of uncertainty in the model analyses.

Question A: The Panel is requested to comment on the utility and suitability of the statistical diagnostic tools used by SHEDS for analyzing model results (e.g., variability analyses, sensitivity analyses, uncertainty analyses).

Results from SHEDS-Wood model runs were analyzed to identify the influence of model inputs on model output. The Agency used a series of sensitivity analyses to identify the model

inputs with greatest influence on inter-individual variation of estimated CCA absorbed doses. The Agency used a similar set of analytical methods to determine the model inputs that contributed most to uncertainty in model output. The Panel commented on the utility and suitability of the methods used to analyze the model results for purposes of sensitivity and uncertainty analysis as presented below.

The Panel concluded that in general the analysis of the SHEDS-Wood model results have been approached in a useful and suitable manner. Since no one single method is best for examining such a complex model, the Agency's use of several different methods to examine relationships between model inputs and outputs was considered by the Panel to be appropriate because various methods can illuminate different aspects of the results. Importantly, the results of the different methods are reasonably consistent, suggesting that the conclusions of these analyses are robust with respect to choice of analytical method. Nevertheless, the results of the variability and uncertainty analyses may be limited by discrepancies between data and choice of statistical tool.

The sensitivity analyses were conducted using a scaling approach and a regression approach. The scaling approach involved perturbing model inputs by two different techniques. In the first technique, the mean value for each model input was increased and decreased by a factor of two from its nominal value. Each input is modified by the same amount relative to its central value and the simplicity of the technique is appealing. However, this same feature limits the interpretation, and hence the utility, of this sensitivity analysis. Scaling up and down by a factor of two invokes a parametric response. In that sense, the range of the variables as measured by say, the standard deviation, is much more relevant. Also, some variables do not display much variability, while others display a considerable range. Thus, one may observe a model sensitivity (or lack thereof in the converse) that is an artifact of simulating an unrealistic amount of variance for an input. For this reason, the SHEDS-Wood developers should consider foregoing the factor of two method altogether where possible. The Panel recognized that in some cases scarce data may necessitate the factor of two or a similar technique, in which case the analysts should consider the potential for the variance of variables to be incorrectly specified.

In the second scaling technique, each model input was perturbed from its central value by plus and minus one arithmetic standard deviation. This technique is similar to the original procedure recommended at the 2002 SAP meeting to take the 16^{th} and 84^{th} percentiles of the distributions to represent what a normal distribution would correspond to plus or minus one standard deviation. The standard deviation scaling technique is appealing because the perturbation is normalized with respect to the variability assigned to the parameter. In other words, the scaling afforded by altering a model input by one standard deviation provides an assessment of the impact over the likely range of the variable. For limited data, or data for which a one standard deviation change would give improper, e.g., negative, results, an alternative non-parametric strategy such as a percentile estimate would be appropriate. This type of non-parametric scaling should be applied to the several variables that the Agency did not include in the sensitivity analysis because the procedure returned illegal values. Non-parametric scaling would be a useful and, in some ways, a more consistent way to assess the contributions of different parameters to overall variability.

The regression approach to sensitivity analysis involved using stepwise regression to analyze associations between model inputs and model output. The model inputs were ranked with respect to sensitivity by their partial R^2 determined from the regression analysis. The regression approach is a more rigorous statistical tool than the two scaling techniques. A principal advantage of the regression approach is that the sensitivity of a model input can be assessed, controlling for influences of other inputs. The multivariate analysis provides a potentially more accurate and useful characterization of the model sensitivities. Regression analysis requires assumptions about distributions of dependent and independent variables – e.g., independence and normality. To the extent that these assumptions are not met, the results of the regression analyses are subject to limitations. The Agency should acknowledge these potential limitations and determine the extent to which their conclusions could be influenced by these factors.

Uncertainty analyses were conducted to obtain insight about the types and sources of knowledge gaps that contribute most to uncertainty about the endpoint of the modeling assessment. For this purpose, the Agency used Pearson and Spearman correlation analysis as well as stepwise linear regression to examine associations between the mean value of model inputs and output. The advantages and limitations of the Pearson and stepwise regression methods, both parametric procedures, are characterized sufficiently in the preceding paragraphs. The Spearman or rank correlation technique may be preferable because the results are insensitive to the distribution of the input variables, except in datasets where many observations have the same value, unlike the inputs and output of SHEDS-Wood.

Some Panelists suggested that a better experimental design could be used for the sensitivity analysis. Fractional factorial designs are appropriate; in particular, fractional factorial designs developed by Taguchi (Montgomery and Runger [2003]; Czitrom and Spagon [1997]) for industrial quality improvement should be considered. A good design will expedite exploration of the factors of the model to determine which are the key factors driving the model. Taguchi designs are appropriate when there are many factors and relatively few interactions between the factors.

Question B: Is the bootstrap approach that is used for fitting uncertainty distributions, which has been revised in response to prior SAP comments, implemented properly, or are there alternative approaches that are recommended?

The Panel concluded that the bootstrap approach is implemented appropriately. Alternative approaches are available for fitting uncertainty distributions from available data. However, in the Panel's judgment, such alternative approaches are unlikely to yield results that are sufficiently different to make an appreciable difference in the overall results. In addition, addressing other sources of uncertainty in the data and model may yield more substantive improvements to the modeling system and its results in this application. For example, the bootstrap approach cannot be used to express uncertainty for which there are few data points.

Question C: Are the uncertainty distributions assigned to chemical and non-chemical

specific model input parameters appropriate?

In cases where the available data are applicable (i.e., specific to the model use) and representative (e.g., an appropriate sample of U.S. children), the uncertainty distributions described in the Agency's background document "A Probabilistic Exposure Assessment for Children Who Contact CCA-Treated Playsets and Decks" are probably reasonable and in general appear appropriate. However, the Panel noted that the August, 2002 SAP recommended uncertainty analysis to include modifying uncertainty about the distributional form of an uncertainty expression, in addition to altering the parameters for a given type of probability distribution function.

In cases where the available data are not specific to their use in the model or representative of the appropriate portion of the U.S. population, then the uncertainty distributions generated by the bootstrap method may not be appropriate. The Panel learned, for example, that the studies used to quantify hand-to-mouth frequency included few, if any, children on public play sets, residential play sets, residential decks, and the soil around them. We also know that absorption rates were based upon animal models exposed to certain concentrations of CCA, yet there appeared to be no consideration of animal-to-human extrapolation or possible concentration-dependent absorption rates. Other examples of this type exist and should be considered by the Agency when conducting this and other uncertainty analyses.

Question D: The Panel is requested to comment on whether the modeling approach and documentation appropriately identify and address critical sources of uncertainty in the model and the resulting exposure estimates. Does EPA's documentation adequately describe the uncertainties inherent in the data used for modeling and the influence of these uncertainties on interpretation of the modeling results?

In general, the Agency's documentation contains a reasonable, although not always adequate, description of the uncertainties inherent in the data and the influence of those uncertainties on interpretation of the modeling results. A more detailed analysis is described below.

The uncertainty bounds described in the SHEDS-Wood exposure assessment indicated that the uncertainty analysis has potentially important limitations. For example, the 90% confidence interval for uncertainty about median LADD of arsenic ranged over a factor of 4 (Figure 37 of the Agency's background document "A Probabilistic Exposure Assessment for Children Who Contact CCA-Treated Playsets and Decks"). This range of uncertainty was surprisingly narrow. The unexpectedly small range of uncertainty may be in part a result of the decision to use only the bootstrap approach to characterize uncertainty and thereby was necessarily limited to parameters for which data were available to support that type of analysis. The Agency should probably include some explanation for this counterintuitive result.

Generally, it is likely that overall uncertainties are understated: (1) influential variables for which no variability estimates were made were also not subject to the bootstrap uncertainty analysis, and (2) any procedure that relies on internal fluctuations within a data set will tend to

incorporate only random error and neglect sources of systematic error among studies, such as unrepresentativeness of the studied population for the target population of exposed children.

To deal with the first problem, the only feasible approach is to use professional judgment (or a formal expert elicitation) to arrive at a reasonable estimate of uncertainty, perhaps informed by estimates of uncertainty made for parameters where more data are available, combined with basic mechanistic considerations. Although *ad hoc*, the use of professional judgment or expert elicitation would eliminate the exclusion of potentially important and highly uncertain variables from the uncertainty analysis. Some examples of potentially important variables not included in the present uncertainty analysis are listed below:

- Average number of days per year that a child plays on or around a CCA-treated public playset.
- Fraction of children with a CCA-treated residential playset.
- Average number of days per year that a child plays on or around a CCA-treated residential playset.
- Fraction of children with a CCA-treated residential deck.
- Average number of days per year that a child plays on or around a CCA-treated residential deck.
- Location-activity diaries.

For the second problem, the magnitude of unsuspected systematic error and procedures for inflating conventional standard-error type estimates of uncertainty have been empirically studied in a series of papers by Schlyakhter (Shlyakhter and Kammen, 1992; Shlyakhter, 1994ab). The basic observation is that as improved measurements of physical parameters become available, the newer values tend to wander outside conventional confidence limits estimated purely from random error much more frequently than would be expected by chance, if the conventional confidence limits based purely on random error were correct. Based on this work, Hattis and Burmaster (1994) have described the pragmatic application of procedures to estimate overall uncertainty (combining random and systematic error) from estimates of variance based on random error alone, assuming that the measurements made are no more free of systematic error than physical measurements of elementary particle properties on which the Shlyakhter comparisons were based. It should be understood that this approach is neither widely known nor widely applied to uncertainties in environmental risk assessments or other types of uncertainty analysis studies. There has also been no systematic effort for environmental risk-related variables to make comparisons similar to those of Shlyakhter of improved measurements of fate/transport/exposure-related parameters to confidence limits estimated from earlier studies. Nevertheless it can be considered as one approach to reduce the persistent problem of systematic underestimation of uncertainties, and can potentially be the subject of empirical research as improved measurements of parameters related to environmental exposures are made.

Finally, the Panel observed that the existing estimates of uncertainty in various parameter distributions offer an invaluable opportunity to explore and calibrate this possible avenue of uncertainty evaluation. If improved representative measurements are now made of key model parameters (as suggested in some detail during the public comments and Panel discussions), this would provide the basis for assessing the degree of underestimation of uncertainty that results

from the techniques applied in this version of the SHEDS-Wood analysis.

Also omitted from the uncertainty analysis is a lack of knowledge about the appropriate scenarios to include in the model and the algorithms (and corresponding data) used to simulate physical events. At least some of these scenarios and algorithms were identified in the materials provided to the Panel. Some examples were:

- Exposures associated with water and mulch.
- Effectiveness of sealants as a function of time, wood condition, and other factors to contain CCA residues.
- Potential for unloading events from the skin.
- Assumptions about arsenic chemical form and oxidation state on availability for transfer of CCA residue to skin and subsequent absorption perhaps associated with leaching suggested by the changing Cr:As ratios.
- Transient changes in exposure conditions that could have a substantial influence on short-term exposures including sanding, sawing, and changes in pH associated with maintenance of decks.
- Absorption fraction approach or a physical model of dermal absorption as described in the Agency's background document "A Probabilistic Risk Assessment for Children Who Contact CCA-Treated Playsets and Decks."

The Panel can only speculate about the influence of these types of uncertainty on the model results without undertaking an intensive investigation. It is clear, however, that additional and potentially critical sources of uncertainty remain to be addressed. Lastly, additional details about the clarity of the uncertainty discussion in the report are required. Tables 14 to 27 need to include the simulation size information in the caption. The concept of "stable" as used in the Agency's background document "A Probabilistic Exposure Assessment for Children Who Contact CCA-Treated Playsets and Decks" with respect to the choice to conduct 189 uncertainty runs should be defined more precisely.

Question E. Does the Panel recommend performing any additional uncertainty analyses to evaluate the impacts of using alternative input distributions on the modeling results (*e.g.*, to address uncertainties in various factors determining the frequency of children's exposures to CCA-treated wood in playsets and decks)?

The Panel agreed that the Agency should conduct additional uncertainty analyses to evaluate the impacts of using alternative input distributions on the modeling results. In particular, the Agency should focus on expressing uncertainty about the model inputs and scenarios listed in the Panel's response to issue 4.D. Methods to assess the impact of data paucity can be suggested. The Panel understands the enormous challenge the Agency would undertake to better understand the key sources of variability and uncertainty in the model inputs.

However, without knowledge of these components of variance, it is very likely that the uncertainty in the estimates made is, itself, underestimated. This is important for establishing the

conceptual framework for characterizing uncertainty and as a result, aids in defining the scope and methods of the analysis. Although additional challenges remain for specifying variability and uncertainty in model inputs, the Panel noted that the current version of SHEDS-Wood represents a substantial and significant development beyond the deterministic models primarily applied heretofore and previously presented to the Panel.

For example, the purpose could be to characterize the entire likelihood function of plausible hypothetical population-based probability distributions for CCA exposure. The current exposure assessment does not appear to have this purpose because potentially important exposure scenarios, exposure-related mechanisms, and parameters were not included in the formal uncertainty analysis.

The current uncertainty analysis is limited to where the data are sufficient to support the bootstrap analysis methodology for characterizing parameter uncertainty. As a result, this strategy has little chance of finding the true range of possible and plausible exposure distributions for the modeled population.

Similarly, the purpose could be to characterize uncertainty associated with relatively data-rich parameters within the historical model framework and CCA-exposure scenarios of SHEDS-Wood. Even though much more limited in scope than the first example, this purpose is fine and clearly has scientific utility. This hypothetical purpose is an approximately accurate description of the uncertainty analysis contained in the report reviewed by the Panel.

Regardless, the Agency should carefully and comprehensively articulate the purpose of the uncertainty analysis. Readers and users of the results should be cautioned against a false sense of assurance about the accuracy of the uncertainty analysis.

Issue 5: Special Model Simulations

A number of special simulations with the SHEDS-Wood model were conducted in order to examine the importance of specific exposure scenarios or the impact of certain input assumptions. For example, some of these analyses included conducting separate simulations for children exposed to public playsets only, modeling exposures of the 7-13 year old age group, and studying exposures of children exhibiting pica behavior. Additional analyses were also conducted to examine the impacts of using data or assumptions about increased GI absorption, decreased dermal absorption, lowering the transferable wood residue concentrations by sealants, and hand washing after play events. The results from these special analyses were not significantly different than the baseline model results, except for the large impact of assuming the use of sealants would greatly reduce wood residues.

Question A. The Panel is requested to comment on the appropriateness of the justifications made in characterizing the key factors or inputs for each of these special simulations. Did the Agency provide adequate technical rationale and justification for its choices for these alternative exposure scenarios or input distributions? Do the results from these special

analyses reflect proper use of available information?

The Panel was generally satisfied that the Special Simulations (see Box below) conducted by the Agency are well justified. The scenarios investigated are logical additions to the overall sensitivity analysis (this question overlaps somewhat with Issue 2, Question B) and are in some cases directly responsive to stakeholder concerns.

Special Simulations

- Access to public playsets only
- Addition of 7-13 age groups
- Addition of soil pica behavior
- Surface residue RBA set to 100% (vs. 27%)
- Dermal availability set to 0.01% (vs. 2-3%)
- Additional hand washing after play
- Wood residues reduced by 90% by sealant
- Wood residues reduced by 99.5% by sealant
- 90% wood residue reduction + additional hand washing
- 99.5% wood residue reduction + additional hand washing

The Panel offered the following additional observations:

Some lack of data to support better analyses is evident in the approach taken to look at children 7-13 years old, in which four scenarios were developed by assuming 25, 50, 75, and 100% of 1-6 year old doses in later years rather than estimating doses specific to older children. CHAD does include activity pattern data for the older group that could be used, although age specific data for some other exposure factors are either lacking or drawn from very small populations.

Table 43 of the Agency's background document "A Probabilistic Exposure Assessment for Children Who Contact CCA-Treated Playsets and Decks" compares contributions of residue and soil dermal contact and ingestion to dose based on a variety of scenarios. The contribution of soil ingestion rises when a 90% reduction in surface residue due to sealing is assumed. This would suggest that sealants do not influence the amount of As or Cr that gets into the soil around the playset or deck. Therefore the scenarios being assessed are sealing after some weathering of the playset or deck has already occurred and not effective sealing of a new installation. This is a reasonable scenario to test, but a more explicit description of the sealing assumptions might be appropriate.

Question B: Do any of the findings from these special analyses necessitate the Agency to consider revising certain scenarios or inputs to the baseline assessment?

The Panel was interested in the issue of non soil pica and mouthing. Comparison of the results of the pica-child short term ADD (p. 116 of the Agency's background document "A Probabilistic Exposure Assessment for Children Who Contact CCA-Treated Playsets and

Decks.") with the all children short term ADD (p. 92 of the Agency's background document "A Probabilistic Exposure Assessment for Children Who Contact CCA-Treated Playsets and Decks") reveals a large increase in dose due to soil ingestion, suggesting that soil pica could be an important behavior. For children who mouth objects at unusually high rates or ingest non food items other than soil, one might expect similarly increased doses due to contact with surface residues. These behaviors might be particularly important in children exhibiting autism or Down's Syndrome (Olson 2003). The Panel questioned whether there are data to support increased hand to mouth activity in certain populations or any data to show increased mouthing activity for certain fractions of children or over certain age spans.

With respect to sealants, the Agency has investigated the effect of very efficient sealing. The Panel suspects that efficiencies of 90% or 99.5% cannot actually be achieved or sustained in the field. A modified scenario that accounts for a gradual loss of sealant effectiveness over time might be considered.

The Agency might also consider simulation of the normal exposures plus increases caused by infrequent events. Such events might include exposure to wood sawdust generated during construction of a new deck or during sanding in preparation for coating, or handling of wet (i.e., inadequately cured) lumber at the time of purchase.

Issue 6: Evaluation of the SHEDS-Wood model results

The Agency has evaluated the probabilistic CCA exposure model results by comparing them to results from other earlier deterministic CCA assessments. In particular, the SHEDS-Wood model results were found to compare well to a deterministic CCA assessment performed by the Gradient Corporation, and SHEDS-Wood upper percentiles compare well to deterministic Consumer Product Safety Commission estimates.

Question A: Has EPA provided adequate documentation of the overall plausibility of the exposure estimates generated by the SHEDS-Wood model for CCA? Are the comparisons with the results of other selected exposure assessments appropriate and appropriately presented? Are there any other types of benchmarking approaches or data to assess the reliability of the overall exposure model or specific model elements?

The Agency's background document "A Probabilistic Exposure Assessment for Children Who Contact CCA-Treated Playsets and Decks" adequately documented six other exposure assessments in terms of the dose equations, input variables, and the levels of estimated exposure. In general, the exposures from these estimates are in the same range as the output from the SHEDS-Wood model. In some cases, this may be due to overlap of the data available for the exposure assessments. The comparison revealed the limitations for comparison in these seven sets of data due to their different approaches. The comparison neither validates nor invalidates the estimates from the SHEDS-Wood model.

A fundamental issue about model comparison is in more precisely defining the purpose for comparison. Model comparison, in part or as a whole, can be one approach to model

evaluation. One approach is to see if those variables that strongly influenced the SHEDS-Wood model (e.g., surface residues and surface-skin transfer efficiencies) are in the other models and bear similar values. Another approach is to model the same exposure scenario based on the same input variables. The assumption is that, if the models used more or less the same inputs, they should have similar results.

However, it was recognized that running CCA exposure scenarios with these models would require substantial resources. Ultimately, comparable outcomes would not necessarily mean that these models accurately reflect real exposures, but simply that they are measuring the same variables in the same way. Alternatively, if the purpose for comparison is to see how the SHEDS-Wood output compares to the estimated CCA exposures that have been conducted so far, as was presented in the Agency's background document "A Probabilistic Exposure Assessment for Children Who Contact CCA-Treated Playsets and Decks", it is not necessary that the various models all have a similar approach.

Issue 7: Overall completeness and acceptability of the SHEDS-Wood probabilistic CCA exposure assessment

EPA has revised the August 2002 SHEDS-Wood exposure assessment after carefully considering numerous comments and suggestions that it has received from various parties, including those from the August 2002 FIFRA SAP members, EPA/ORD and EPA Program Office peer-reviewers of the preliminary draft September 2003 report, and from the general public and other external groups.

Question A: In addition to the comments and suggestions already offered by the Panel members under the specific issues raised previously, considering the availability of data and information, does the Panel recognize any critical gaps in information or methodologies that still need to be addressed for the CCA exposure and dose assessment?

The Panel commended the Agency on an overall conscientious effort to respond to the various suggestions made by the Panel at the previous FIFRA SAP CCA-treated wood meeting. Overall the forms used by the Agency to describe the distributions are reasonable, and the Panel believed that other reasonable distributional forms are unlikely to appreciably alter the principal findings. The Panel also believed that the Agency's use of bootstrap uncertainty methodology fairly reflects the Agency's sense of the statistical uncertainties in the data they have available (although, as discussed in Issue 4, there are still reasons to expect that overall uncertainty is likely to be understated).

During the public comment presentation, one important observation that emerged was the presence of CCA residues apparently from recycled treated wood products in "mulch" used in playgrounds. This seems to be a worthy subject for more in-depth risk evaluation and possible advice to the public on desirable sources of materials for use in cushioning falls in public and home playgrounds.

Some Panel members expressed uneasiness with the judgments used to arrive at estimates

for some parameters. To some, the mean of 126 contact days seemed high relative to expectations for a general population. Further discussion clarified that the study was not meant to reflect the general population of children but children with relatively frequent and consistent contact with CCA-treated playsets. For future communication, it might be reasonable for the Agency to either estimate the actual fraction of the general population that is intended to be represented in the analysis, or at least to give some greater emphasis to the fact that only a minority consisting of particularly high-contact users is intended to be the focus of the analysis and results.

There also was concern about whether the measurements and model assumptions accurately reflected the likely transfers that would occur as a result of repeated touching of the same surface. In particular, there was concern about whether the model's assumptions about the transfers from treated wood that would result, given reasonable intensity of playset use by many children over the years, would be greater than possible based on mass balance considerations.

At least one Panelist believed that some additional clarification would be helpful to the reader to prevent misunderstanding of the Agency's use of "Warm" versus "Cold" scenarios. This Panelist's impression was that the Agency seemed to waiver between applying those terms strictly as upper and lower bounds of the exposure data versus actually attributing them to the effects of different climate—leading to various misunderstandings /comments/criticisms by reviewers. While in some cases it does make sense to assume that a warm climate will increase exposure (i.e. number of days outside and amount of skin exposed), in other cases there is little evidence the climate is a major factor (although it might be). In the further application of this model to risk assessment, it might be more useful to use terms such as "upper bound" and "lower bound" and then apply the input data accordingly, regardless of its geographic derivation (i.e. soil arsenic data). From separate studies, a mean value of 34 mg/kg is used for playsets in "warm" climates, while a mean of only 3.7 mg/kg is used for "cold" climates. In other words, they are different by nearly a factor of 10. While this does at least correspond to the intent of having "warm" and "cold" correspond to upper and lower bounds, the opposite trend is noted for decks. For decks, a mean of 41 mg/kg is used for the "warm" climate and 84 mg/kg is used for the "cold" climate. This conflicting combination of soil arsenic concentration is likely to reflect the high variability that occurs within and between sites when sampling for arsenic leached from treated wood, and is not necessarily a result of "warm" versus "cold" climate. Soil arsenic concentrations adjacent to treated structures are a function of many factors including climate, soil characteristics, wood species and wood surface area. The single largest source of variability might well be the surface area of treated wood that drains or drips into a certain area. This Panelist therefore suggested that in this case, the Agency ignore the geographical location of the soil samples and use the lower values for the "cold scenario" and the higher values for the "warm" scenario.

Other Panel member comments indicated a need to add an unloading mechanism of elimination of residue from the hands through the touching of uncontaminated surfaces between playset contacts and mouthing events. In general, the Panel suggested that it would be desirable to clarify the calculation of maximal dermal loading, by including some tables to quantitatively describe the distributions of this type of intermediate calculation result (which is difficult to

discern from the inputs and ultimate outputs alone). This would be an aid for reviewers in judging the plausibility of several assumptions working together.

Finally, in the light of the public comments on the difficulty of achieving the high sealant effectiveness levels used in some model runs, Panelists suggested that the Agency might consider some adjustments in these assumptions.

Issue 8: In the study by Nico et al. (2003), X-ray absorption spectroscopy (XAS) was used to determine the chemical and structural state of arsenic and chromium molecules in CCA-treated wood residue samples. Based on the results of their analysis, Nico et al. (2003) determined that arsenic and chromium formed a "chemical complex bonded to the wood structure." Based on this study, the dominant oxidation state of the two elements is As(V) and Cr(III), and the local chemical environment of the two elements is best represented as a stable Cr/As cluster consisting of a Cr dimer bridged by an As(V) oxygen ion. Nico et al. (2003) also maintained that this chemical complex was quite resistant to leaching.

Question A: The Panel is requested to comment on the Nico et. al. (2003) study and particularly on the arsenic and chromium chemical complex from CCA treated wood surface residue, and whether the Panel believes that the chemical complex is formed during the fixation process. What is the meaning of this complex cluster formation to the current risk assessment.

The Panel concluded that the Nico study, while important in the understanding of the nature of the Cr and As fixation in CCA wood and of the nature of the complex in wood particles, may not represent dislodgeable residues in general. The Panel's responses to individual issues related to this question are provided below.

Is the complex formed during the fixation process?

There is little doubt that chemical reactions occur between arsenic and chromium during fixation, and that these reactions greatly diminish the solubility of the arsenic in CCA treated wood. The Nico et al. (2003) study does not attempt to address the mechanism of formation of the complex. However, given the complex's almost-complete dominance of the species present in the CCA wood (both new and aged) and in the American Chemistry Council (ACC) "Residue" preparation samples (to be called ACCR), it is likely that the complex is the major product formed during wood treatment.

Is the complex identity certain?

The specific complex described by Nico et al., is consistent with the spectral data. However, the authors should clearly indicate that their proposed cluster structure is just one possible example of a longer-range structure (second coordination sphere) and the real structure is probably much more polydisperse than this suggests. The cluster structure proposed is not a unique solution to fitting the EXAFS (Extended X-Ray Absorption Fine Structure) data, and other structures should be considered to give a sense of the uniqueness (or lack thereof) of these

long-range interactions.

The most common mistake made when analyzing EXAFS data is the failure to realize that molecular models that provide good fits to the EXAFS may be only one of a number of models that provide equally good fits. That is, the uniqueness of a given simulation can almost never be proven. The other important realization is that XAS always provides an average environment and cannot be used to uniquely identify structural components of a mixed population. Often missing, this key fact causes researchers to propose homogeneous structural environments when a heterogeneous sample is analyzed.

Also, an apparent consistent fluctuation of Cr/As ratios between lower and higher-density wood areas suggests some variation in speciation between the areas.

It is likely that there are additional fixation products, at least for chromium, given the reactivity of chromium and the range of possible reactive sites within the wood structure. Studies are also in general agreement that when the fixation reactions are complete, less than 1% of the chromium in the wood is hexavalent. There have been fewer studies confirming the valence state of arsenic, and the Nico et al. study is important in this regard. However, further work to characterize the chemical nature of the As/Cr complex, particularly those that are picked up on skin from CCA-wood surfaces, would contribute to the risk assessment process.

What is the meaning of this complex cluster formation to the current risk assessment?

The study is an important advance in an understanding of the nature of the speciation or structure of fixed Cr and As in CCA-wood. Arsenic in CCA treated wood has low solubility, the arsenic is primarily pentavalent, and the chromium is trivalent. The Panel agreed that this complex (regardless of minor variations in structure) which is bound to the wood structure, is liable to be of limited bioavailability compared to As in solution. This conclusion is strengthened by the near-identical spectra in new and aged wood samples and in the ACCR. This indicates that the complex is quite stable—at least while it is incorporated in the wood structure. It must be remembered that ACCR appears to be mostly a dried suspension of fine CCA-wood particles as presented as a public comment by Battelle for the Wood Preservative Science Council "Chemical Characteristics and Morphology of Particulate in Dislodgeable Residue." Thus, ACCR would not be expected to exhibit significantly different speciation from uneroded CCA wood in an EXAFS study. There is some evidence (as will be presented in the Panel's response to Issue 9) that a significant fraction of the As in ACCR can be solubilized in the GI tract.

Other considerations

An important question which was not considered is whether the ACCR preparation adequately represents those chemical specie(s) that are leached from CCA-wood to soil, or, more importantly, those chemical species that adhere to skin—the most

significant route of exposure to arsenic. The reason for this concern is that leaching studies of CCA treated wood consistently report that a lower proportion of CR than 2 moles chromium (Cr) per mole Arsenic (As) is released from the wood. During weathering, UV degradation and leaching may release forms of As that are more soluble while releasing less Cr. The result is the soluble part of residue has a lower Cr:As ratio than residue particles or bulk wood. This hypothesis is strengthened by the ACC wipe study: residue obtained by the block wipe and coupon wipe method had a higher Cr:As ratio than that obtained by gentler hand wiping, suggesting that the more aggressive wiping methods removed more wood particles, thereby raising the overall Cr:As ratio.

The Cr:As mole ratio of 2 predicted by the dimer model is consistent with the 2.2 ratio reported in their aged treated wood, and somewhat consistent with the 1.7 ratio in the ACCR residues. Stilwell et al. (2003) reported an average mole ratio of about 2.2 in dislodged residues, and the ratio was 1.7 ± 0.4 in residues analyzed by RTI. However, the ratio found on hand residues in the ACC study was only 1.3 ± 0.3, suggesting that hand contact with the wood surfaces dislodges fewer wood particles containing the bound As-Cr complex and more of an unbound fraction of arsenic.

Thus it is possible that some arsenate detaches from the Cr dimer, where it is preferentially leached from the wood. The driving force behind the dissociation of the dimer could be UV radiation, and acidic rainwater. In Nico et al. the potential for reactions with acid rain was mentioned. Some examples showing that the Cr/As mole ratio is less than 2 can be found in a review of leaching by Kingston et al. (2001). In this review, the Cr:As mole ratio, computed from data based on the flux ($\mu g/cm^2$/day, Table 5), was 0.45, 0.36, 0.29, and 0.02. In a paper by Lebow et al. (1999) the long-term release rate of Cu, Cr, and As was given. The computed Cr/As mole ratios computed from table 7 in this work were 0.16, 0.48, and 0.23. Lebow also measured leaching of new wood under simulated rainfall conditions (Lebow et al. 2003). In this case the Cr/As mole ratio was 0.34. In soils, the Cr/As mole ratio (after background correction for Cr and As) was 0.5 in studies by Stilwell and Gorny (1997), while the mole ratio was 0.7 in a report by Zagury et al. (2003).

Therefore, the erosional material represented by ACCR may not adequately represent the longer-term effects of rainwater, sunlight (UV), and diffusional components. Stilwell et al. (2003) had proposed a model to explain a "rejuvenation" effect noted on the wood surface—a slow replacement of dislodgeable residues after removal by leaching. This model evokes erosion, diffusion and rainwater effects.

Any residue description would have to account for the observed preferential release of As in the leachate and the soils. One explanation for the discrepancy between the mole ratios is that the actual surface layer, when exposed to environmental conditions, could contain both soluble and relatively insoluble As fractions.

Issue 9. Casteel et al. (2003), reported that the relative bioavailability (RBA) of dislodgeable wood residue is 27%. This value is significantly lower than the default value of 100% that is usually employed when reliable site-specific data are lacking and also lower

than the RBA value recommended by the SAP 2001. The result of this study indicates that the arsenic in the dislodgeable arsenic material is not as well absorbed as soluble arsenic.

Question A: Does the Panel agree that, in light of the Casteel study and the Nico study discussed in issue 8, the Agency should use 27% for the RBA to estimate the bioavailable dose.

As stated in Issue 8, there is little doubt that arsenic in CCA treated wood is less soluble than it would be in a form such as sodium arsenate. The form and solubility of arsenic in the American Chemistry Council residue sample described in the Panel's response to Issue 8 (ACCR) is less clear, although the results of Nico et al. (2003) suggest that it is similar to that of the treated wood. Casteel et al. (2003) measured urinary excretion of As in juvenile swine fed ACCR as compared to soluble As(V) arsenate at similar total As dosage. They reported a urinary excretion factor (UEF) of 23 $\pm$ 1%, and a relative bioavailability (RBA) compared to arsenate of 29 $\pm$ 3 %.

The Panel concluded that: (a) inadequacies in the study design; (b) the likelihood that actual residues found on skin are more bioavailable than ACCR; and (c) the likelihood that ingested ACCR is more bioavailable in pigs than in humans, leads to conflicting possible interpretations of the Casteel et al. study. Thus, due to these deficiencies, the Panel could not suggest a value for the RBA of CCA-wood residues dislodged by skin.

Since ACCR is essentially particulate CCA-treated wood, it is expected that the RBA would be low. Residues from other sources could behave differently. The Panel is concerned that the residue used in both these studies may contain a higher proportion of wood particles than would be obtained by a hand wipe. The residue was generated by brushing the wood with a soft brush and then filtering-out the larger material. Comparisons of hand-wipe data to that from other forms of wiping (ACC 2003) indicate that non-hand wipes are more abrasive. It is possible that residues on a human hand may contain a lower proportion of wood particles and a higher proportion of soluble arsenic.

The Panel provided additional comments on the ACCR feeding study and possible underestimation or overestimation of RBA CCA-wood dislodgeable residues:

1. A 1-4 year old deck is not a typical neighborhood deck. In a public comment provided by Helena Solo-Gabriele (University of Miami), longer weathering results in a greater leakage of As(III) from the CCA-treated material. Older decks may yield different results.

2. Not all relevant methylarsenic species standards were checked. Methylarsenic species standards were not checked as part of the As methods validation. Do pigs metabolize As to form methylarsonous acid, dimethylarsinous acid, or trimethylarsine oxide? What is the recovery of the method for these species? For example, trimethyarsine oxide recoveries from urine can be poor when acid digestion is used.

3. In general, under steady-state conditions, urinary excretion patterns of As are representative of GI absorption. Previous studies in swine suggest that the steady state for soluble inorganic arsenic species is reached after approximately five days. The metabolic patterns, including pharmacokinetics of urinary excretion and tissue distribution for As species in dislodgeable residues or CCA-contaminated soils have never been characterized. The calculation of RBA in Casteel et al.'s study is based on the assumption that steady-state was reached for the metabolism of As in all treatment groups, i.e., those fed with arsenate and those fed with various doses of CCA-treated materials. This assumption is, however, based on a limited number of time points (3 for the dislodgeable As study and 2 for the soil study). In addition, the urinary excretion patterns indicate that steady state was not reached in animals treated with the high dose (120 ug/kg/d) of As-contaminated soil and in animals treated with the low dose (30 ug/kg/d) of As in ACCR (Fig. 4-2 in both papers). The steady state was not reached in animals fed arsenate (in dislodgeable As study) as indicated by increasing urinary excretion of As between the day 6 and 11. These discrepancies undermine the author's conclusions and contribute significantly to uncertainties regarding the validity of the calculated RBA values for both dislodgeable As and As from CCA-contaminated soil.

   The Panel proposed that the steady state conditions for metabolism of As from dislodgeable residues and contaminated soils should properly be evaluated before accurate RBA values can be determined. Obviously, examination of absolute bioavailability would provide more valuable information. This may require examination of biliary and fecal excretion and tissue distribution patterns in animals chronically exposed to dislodgeable residues and CCA-contaminated soils

4. Speciation of As in the urine should have been performed to provide basic information about metabolism of both As treatments. For example, higher urinary levels of As would indicate that methylation is suppressed and consequently greater amounts of As species are retained in tissues.

5. The Panel was unable to ascertain, from the information given, the relationship between the concentrations of metals in the ACCR and the surface area of the boards extracted. This should have been easily calculated from the total area of the boards washed/brushed, and the final mass of material after rotary evaporation. Thus the Panel could not relate the doses used to the risk assessment scenario.

6. Compared to humans and other monogastrics, pigs have a more complex lower intestine that allows for dietary fiber fermentation. Since the proposed lignin complex model by Nico et al. (2003) in ACCR has lignin (cellulose) as an integral component, pigs would be expected to metabolize this complex within the intestine more efficiently than humans. In addition, pigs have a much slower gastric emptying time than humans, which increases residence time with gastric acid. Thus, pigs tend to have a higher bioavailability of slowly eroding drug dosage forms that have low bioavailability in other species. Therefore, the bioavailability of ACCR in pigs is probably greater than in humans (Martinez et al. [2002]).

7. In Figure 3-1 of Casteel, there was an assumption in the calculation that Ku (the fraction of absorbed As which is excreted in urine) is the same for compounds x and y. This is not necessarily the case.

Issue 10: In the 2001 SAP meeting, the Panel cited the research of Wester et al. (1993) as a source of the dermal absorption rate of soluble arsenic in water and soil. The Panel recommended using a 2-3 % dermal absorption rate for arsenic residue on the surface of wood. Recently, a preliminary study by Wester et al. (2003) has been submitted by the same laboratory compares the dermal absorption of arsenic in CCA-treated wood surface residues with arsenic in water solution. Although the Agency has not received the complete results of this study (e.g., the recovery of the arsenic in the urine of the animal given IV dose of arsenic), the preliminary results of this study indicate that the dermal absorption of 0.01% from wood surface residue was approximately two order of magnitude lower than the results in water. The dermal absorption from this study was based on urinary arsenic data following application of arsenic in CCA-treated wood residue that had been weathered by the environment.

Question A: Taking into consideration the Nico et al. study mentioned in issue 8, the Panel is requested to comment on whether this new study conducted by Wester et al. provides a more appropriate estimate of dermal absorption from contact with CCA-treated wood surfaces than the earlier 1993 Wester et al. study.

Panel Summary

No quantitative estimate of dermal availability from ACCR can be derived from the 2003 Wester et al. experiments. That study therefore represents insufficient grounds for alteration of the dermal bioavailability assumption used in SHEDS-Wood. The Panel noted that the current default dermal availability used by the Agency (a Beta distribution with mean and median of about 3% per 24 hours) falls closer to the low end of the 2-8% range of availability of inorganic arsenic that would be derived from the 1993 and 2003 Wester et al. studies if correction by intravenous response is assumed appropriate for dermal application of inorganic arsenic; that it is similar to an adjusted LOD for the 2003 ACCR experiments, and that the form of arsenic transferred to the skin of persons contacting decks and playsets is unknown.

Detailed Review of the Panel's Analysis

Some issues related to bioavailability of arsenic in general and interpretations of the Nico et al. study in particular were discussed in the Panel's responses to Issues 8 and 9. Therefore only a brief summary is required here. Generally if arsenic in the CCA-treated wood residue (i.e. ACCR as defined in the Panel's response to Issue 8) is bound in some way to lignin, as is suggested by Nico et al., a reduction in availability would be expected. The apparent reduction in oral bioavailability of arsenic in ACCR relative to soluble arsenic reported by Casteel et al. is also supportive of this conclusion. However, as noted in the Panel's responses to Issues 8 and 9, some questions arise with respect to estimation of the magnitude of reduction in dermal bioavailability that might be expected:

• The extent to which ACCR is representative of material transferred from CCA-treated wood to skin is unknown.

• XAS does not permit unambiguous characterization of heterogeneous matrices and therefore the Nico et al. results cannot rule out availability of some of the arsenic in ACCR even if some is bound tightly to lignin.

• Differential ratios of As to Cr in CCA-treated wood of varying ages, leachate and sub deck soils reported in the literature suggest that some arsenic is released from CCA-treated wood.

• In a presentation to the Panel, Exponent reported that sweat extraction of arsenic from ACCR produced greater release of arsenic than did extraction of two weathered CCA impacted soils. Since arsenic in weathered soils would not be considered completely unavailable, it appears that whatever binding of arsenic does occur in CCA-treated wood is either not complete or not irreversible.

The Panel therefore views the appropriate question to be whether or not the 2003 Wester et al. data can be used to quantitatively estimate the dermal availability of arsenic transferred from CCA-treated wood to skin.

Superficially the 2003 Wester et al. data show mean (n=3) absorptions of 2.8% from soluble arsenic (H_3AsO_4) and 0% from ACCR. Wester et al. assert that the new soluble arsenic result (obtained following analyses of urine by ICP-MS) is essentially the same as reported in 1993 (means [n=4] of 2% from high dose and 6.4% from low dose, obtained using radio-labeled arsenic) and argue that that outcome validates the 2003 ACCR results. It should be noted that the 1993 results were obtained following 24 hours of exposure whereas the exposure duration in the 2003 study was 8 hours. Therefore the more recent soluble arsenic result translates to greater than 8% absorption over 24 hours.

The Panel finds three areas of concern with respect to the 2003 Wester et al. study. These involve generic experimental issues, the ACCR-skin contact scenario, and the pharmacokinetics of absorbed arsenic.

Generic issues include sample size and absence of a mass balance. The very small sample size employed (n=3) limits the statistical power of the experiments. Larger sample sizes are typically required in other regulatory environments. Failure to conduct a mass balance was necessitated by selection of an *in vivo* primate protocol. The Panel views lack of a mass balance as a significant shortcoming given other concerns discussed below.

Concerns regarding the skin contact scenario involve intimacy of contact and potential layering effects. Wester et al. assume that the methods employed in the 2003 study for soluble arsenic and ACCR are the same and that correspondence of the 1993 and 2003 soluble arsenic results therefore validates the 2003 ACCR protocol. Intimacy of contact between arsenic in aqueous solution applied 5 $\mu L/cm^2$ and skin is reasonably assumed. Intimacy of contact between ACCR and skin is less certain. *In vivo* investigation of dermal absorption from solid phases is

inherently difficult and, when conducted in non-human surrogates, inevitably involves adoption of some degree of scenario artificiality to avoid in vitro artificiality. Because behavior of non-human surrogate species is not easily controlled, retention of material on the skin for meaningful exposure times presents significant challenges. Application sites must be protected from loss due to sloughing, incidental abrasion, or licking or scratching by the subject animal. Investigators attempting such experiments usually apply some combination of animal restraint and physical covering of the application site. Tight covering is desirable to ensure contact, but may lead to undesirable occlusion effects. Loose covering will not preclude sloughing and loss of contact.

Transport of contaminants from an external solid phase into skin occurs by one of three mechanisms: 1) direct contact (if the agent of concern is on the surface of the solid phase and that same solid phase surface is in intimate contact with skin, direct transfer may occur); 2) diffusion in liquid-filled (usually aqueous) pore spaces; or 3) diffusion in vapor filled pore spaces. Solid phase diffusion is typically very slow with respect to realistic exposure periods and therefore negligible. Compounds with negligible vapor pressures can only be transferred by direct contact or liquid phase diffusion. Since even a very thin air gap between external medium and skin represents an absolute barrier to transport of non-volatiles (such as inorganic arsenic), a vertical configuration, as was employed by Wester et al., is generally ill-advised.

In the 2003 experiments, contact was allegedly assured by application of Tegaderm® and Spandage® coverings. This indicates that the research team was at least somewhat aware of the contact issue and photographs of the experimental protocol shown to the Panel do appear to reveal good contact between the ACCR and the skin. However the contact area was 100 cm^2 which represents a large fraction of the abdomen of a rhesus monkey. It is likely that the covering extended to the rib cage and hip bones of the monkeys. Given that reported absorption was 0%, visual appearance may or may not be sufficient evidence of intimate contact in this case. Although the investigator said the abdomen was shaved, from the photos it was unclear how much hair was evident. No liquid solutions were placed on the abdomen as a control.

An additional aspect of the contact scenario that must be addressed if results are expressed as percent absorbed is layering. Wester et al. applied 4 mg/cm^2 of ACCR to the monkeys' abdomens. They assert that this would be roughly a monolayer based on an EPA estimate (EPA 2001) of monolayer coverage at 5.4 mg/cm^2 for silty clay. There are two flaws in this argument. First, the Agency used average particle size to calculate monolayer loading which will lead to overestimation of the mass required to achieve coverage. Second, tests of ACCR indicate that it is primarily woody material rather than soil. Wood has a much lower specific gravity (s.g. $\approx$ 1) than soil (s.g. $\approx$ 2.65) and therefore will provide surface coverage at much lower mass loading than soil given the same particle size distribution. Given nominal particle diameters (estimated from particle cross sectional areas) reported by Battelle (2003), ACCR probably provides monolayer coverage at a loading less than 1 mg/cm^2. Therefore the applied load in the 2003 ACCR experiments represents 4 or more layers and the observed percent absorption requires adjustment upwards. (The presentation of the Wester et al. results to the Panel included photographic evidence of layering. When the Tegaderm® patch was peeled back from the abdomen of one monkey, both the patch and the skin appeared to remain covered with ACCR. This suggests at least 2 layers.) Since the observed result was nominally 0%, but

actually less than limit of detection (LOD), the effective LOD must be adjusted upwards. Wester et al. report the LOD as 0.02 to 0.2%. Assuming no other problems with this estimate, it should be multiplied by 3 to account for 24 hour rather than 8 hour exposure and an additional factor of 4 or more to account for layering. Therefore an adjusted upper estimate of the LOD is greater than 2% per 24 hours and similar to the existing EPA default assumption.

The final concern involves the pharmacokinetics of arsenic in rhesus monkeys. Wester et al. adjusted both their 1993 and 2003 results using urinary recovery of arsenic following intravenous injection of soluble arsenic. It is unknown whether this adjustment is appropriate following dermal application in general as binding of arsenic by keratin in skin may delay excretion or following possible dermal absorption of complexed arsenic in particular as the fate of complexed arsenic in the body might be different than that of inorganic arsenic. Given these uncertainties, and the failure to conduct a mass balance, the ultimate disposition of arsenic in the 2003 Wester et al. experiments should be viewed as unknown.

Issue 11: In the 2001 SAP meeting, the Panel recommended that a biomonitoring study be performed on children who are normally exposed to CCA-treated playground equipment and decks. The Panel recommended that the study should be designed according to well-accepted epidemiological principles, including adequate sample size, to resolve the issue of whether there are substantial exposures to children from arsenic residues after playing on decks and playsets. The Panel indicated data from such a biomonitoring study could be directly used in the risk assessment and could be used to validate the exposure assessment model. Recently, a proposed protocol for a pilot study was submitted to OPP for peer review; this proposed protocol is an attempt to determine if changes in exposure to arsenic can be assessed by examining changes in the urinary excretion of arsenic. EPA has provided the Panel with a copy of the proposed protocol for the pilot study. In summary, the proposed pilot study will determine whether a significant difference in urinary arsenic can be discerned when a population of children are switched from arsenic-containing tap water to an essentially arsenic-free source of drinking water.

Question A. The Panel is requested to comment on the strengths and limitations of the approach to be employed in the proposed pilot study to help resolve the issue of whether there are substantial exposures to children from arsenic residues after playing on decks and playsets. In particular, please comment on the feasibility, the potential confounding background sources from the statistical analysis, the sensitivity and accuracy of analytical method for quantification of arsenic in urine to detect changes, the determination of intraindividual variation and interindividual variation based on the current knowledge of exposure; and any other aspects of the proposed pilot study that might affect its utility.

Introduction

In the 2001 SAP meeting, the Panel recommended that a biomonitoring study be performed on children who are normally exposed to CCA-treated playground equipment and decks, with the objectives of obtaining measurements of actual exposures, which could be used in risk assessment and to test the exposure model. Issue 11 addresses this issue. To quote: "The Panel recommended that the study should be designed according to well-accepted

epidemiological principles, including adequate sample size, to resolve the issue of whether there are substantial exposures to children from arsenic residues after playing on decks and playsets. …" In response to the 2001 SAP, a proposal for such a study has been submitted to the Agency for review. The proposed work is now summarized briefly.

The proposed pilot study (the Pilot Study) will investigate the effect of elimination of the intake of As-containing drinking water on the total urinary As concentration in a group of young children. The Pilot Study will take place in Albuquerque, New Mexico, a location with levels of As in drinking water reported to be approximately 15 μg/L. Using an expected intake of 0.5 L/day of water from municipal sources, in their oral presentation, the authors of the protocol claimed that the expected intake of As from drinking water approximates potential intake experienced through contact with CCA-treated wood products given as "several" ug/day. It is hypothesized that if differences in urinary arsenic can be seen in the drinking-water based approach, then it is feasible that such an approach can be used in assessing CCA-related dose and dose differences experienced in mitigation strategies.

Conclusions and Recommendations

The Panel concluded that the proposed biomonitoring study by the Wood Preservative Science Council, as it stands, is not responsive to the 2001 SAP request. It is more appropriately a "Preliminary Study" in which data of some potential utility may be gathered, but which in no way assesses exposures or doses likely to be experienced by the target group: children coming into contact with CCA-treated wood products. The study proposal as presented is deficient in many ways, some of which may be matters of the level of detail presented. The Panel has identified a series of major deficiencies, followed by a longer list of minor deficiencies that should be assessed prior to implementation. The Panel believed that, if implemented as proposed, results are unlikely to be reliable, meaningful, or useful with respect to improving an understanding of factors affecting CCA-related As exposure and absorption. Finally, the Panel questioned whether the preliminary study could be carried out successfully to address the goals mentioned.

It is the Panel's recommendation that a proposal for an appropriate pilot/preliminary study responsive to the recommendations of the 2001 SAP be discussed before implementation by all stakeholders– the public, EPA, and industry and re-fashioned to be more responsive to all needs. After receiving input from these three groups, a new study design should, if appropriate, be amended so that it may be implemented in a way to provide information useful to all parties and reflective of the need to understand exposure of children from contact with CCA-treated wood.

The willingness of the regulated industry to entertain outside peer-review in this matter is encouraging as each stakeholder will be involved in various study components. With more thorough peer-review, including involvement of EPA SHEDS-Wood personnel, a re-designed biomonitoring study could be an excellent source of information on actual levels of exposure and absorption, and be used to improve the SHEDS-Wood model.

Detailed Review of the Panel's Analysis

It needs to be pointed out at the outset that the study as presented to the Panel is not a pilot study of the biomonitoring study proposed by the 2001 SAP. A pilot study is essentially a "study in miniature" which, using a small sample of subjects, tests the full range of procedures proposed to be used in the main study, from subject recruitment right through to data analysis. The pilot study should be carried out in the population that is intended to be the main study population. As any study fulfilling the recommendation of the 2001 SAP meeting would need to involve children exposed to CCA-treated wood, the proposed study cannot meet the requirements for a pilot study of the proposed biomonitoring study. Having established that, the next question is whether the proposed study, which is more in the nature of a feasibility study or a preliminary study, could contribute usefully to the development of a biomonitoring study.

The Panel believed that the study as designed would offer little useful preliminary data for a biomonitoring study of children who come in contact with CCA-treated wood and is, therefore, not responsive to the SAP request from 2001. Specifically, it is posited by the authors of the study that the length of a washout period for detecting a reduction in arsenic exposure from elimination of exposure to CCA-treated wood could be inferred from the length of a washout period for reduction of arsenic intake from drinking water. Arsenic found in drinking water is almost exclusively inorganic arsenic, while As exposure from CCA-treated wood products and potential contamination associated with such products consists of a complex mixture of CCA, CCA-wood complexes, inorganic and, perhaps, organic As species bound to soil, and other forms. However, we do not yet know which, if any, of these forms is actually absorbed into the body when exposure occurs. If they are absorbed, it is unlikely that all of the forms discussed above will be equally eliminated at equal rates via the urinary pathway and it is nearly certain that they would not all be eliminated in the same manner or at the same rate as As ingested in drinking water. The hypothesized decrease in total urinary As after the "washout" period may well reflect the decreased As exposure from the consumption of As-containing drinking water. However, the reasoning behind focusing on this approach is not clear. For example: would the absence of a decrease in excreted urinary arsenic suggest that the CCA component of the exposure is more significant than that associated with drinking water? How would one draw this conclusion from the data collected? If this is not the conclusion to be drawn, what is? There seems to be no hypothesis relating the results from this study to a true pilot study of CCA-related exposures.

In addition, Albuquerque has relatively high levels of As in its drinking water supply. It is likely that exposures to As from contact with CCA-treated wood are comparatively small. If the clearance rate of As is related to body burden then, even if As absorbed from CCA-treated wood is in the same form as in drinking water, results of this study will be inapplicable to a biomonitoring study involving CCA-treated wood exposure.

In an ideal approach, a pilot study that is aimed at examining exposure to As from CCA-treated wood would seek to assess concurrent exposures to As from other environmental sources. One would strive to fully take into account intake of all arsenic-containing foods, e.g. rice, grapes, grains, etc., in addition to the intake through drinking water and fish, in an effort to assess the impact of a reduction in As intake through reduced contact with CCA-containing material. This might be modeled in the manner suggested in the proposal through removal of

As-containing water from the diet. However, this is still artificial in that As intake through drinking water in no way mimics intake through contact with CCA-containing wood products. Therefore, one should collect data on both food and water consumption through the study period.

This discussion raises the question of the utility of the study as designed. Consider two similar questions: 1) If a reduction in urinary As levels is measured, what information that is useful or relevant to CCA-based arsenic exposure will be obtained? It is the Panel's belief that little useful knowledge will be gained. The study would indicate that small differences in As exposure might be measured using a urinary As marker. However, the form of the As to which the population is exposed is not necessarily informative in terms of what would happen following exposure to CCA-treated wood. Also, the levels of exposure in Albuquerque are not necessarily relevant to a study of children exposed to CCA-treated wood, particularly if the rate of excretion is dependent on the level of exposure; 2) If there is no detectable reduction of urinary As, what implications can be drawn concerning CCA-based As exposure? For reasons to do with the unknown form of the As absorbed following CCA-treated wood exposure (ACCR as presented by the Panel in Issues 8 and 9), it is the Panel's belief that extrapolation of the results to CCA-related As exposure is tenuous at best.

Below in bulleted form are specific Panel comments on the proposed work. These comments are divided into ***Major Problems*** and ***Minor Issues.*** The former represent problems severe enough to call the entire study into question while the latter represent small flaws, questions, or need for clarification that would not preclude the study from being implemented, but should receive attention. The major points are discussed in somewhat more detail compared to the minor issues. The reader is cautioned that the over-arching problems outlined above still exist. The points made below address specific problems or flaws in the design of the Pilot Study as developed in the document "Arsenic Biomontoring Pilot Study" provided to the Panel for review.

Major Problems

- **Design, Statistical and Quality Assurance Issues**

    - The Pilot Study is to be done in Albuquerque, New Mexico, a site that is not a good choice for a large-scale investigation of the effects of CCA-related exposure due to the relatively high levels of arsenic in the water supply. The Panel strongly suggested that any pilot-level investigation be done in an area expected to be the location for the final study.

    - How will the results of the Pilot Study be used to address the feasibility of the main study? If this study is successful, what caveats must be considered prior to commencing the main study? The answers to these questions are not delineated in the proposed work.

    - Subject Recruitment and Sample Size
        - The Pilot Study calls for a sample of "…up to 40 children…" What does this mean? Is 40 the target or the maximum number? Also in this regard, a discussion of statistical power should be presented. During the public

comments period, the Panel was encouraged that the designers of the study are thinking about the implications of the small sample size on the study's ability to address the specific problems at hand.
        - Similarly, power calculations should be presented for the number of children (5) that will provide a second sample. Is this number sufficient to address the "reliability" of the first morning void samples? No evidence has been presented that suggests how such data can be manipulated to assess the reliability.
        - Multiple recruits in the same family could be problematic in that metabolic/excretion rates may be correlated among family members due to genetic similarities. If more than one child per family is used, appropriate statistical methods would need to be used to adjust for possible intra-family correlation and the power calculations would need to take this into account.

    - What is known about the temporal variability of As in Albuquerque drinking water on times scales of one week? Is a single sample sufficient? Is it necessary to take samples at each home? Are homes different if all are on the same municipal water supply? Such preliminary data should be assessed prior to defining a protocol.

    - More description of the QA samples for the arsenic analysis, including numbers of blanks, replicates, etc., is needed.

    - Storage of lab notebooks, sample logs, etc. for only one year is unlikely to be sufficient. More likely, five years will be needed to comply with GLP requirements.

- **Institutional Review Board (IRB) Related Issues**
    - The present informed consent and ethical structure of the pilot is not optimal. Any attempt for stakeholder revision of this pilot/preliminary study, and indeed, peer review for solicited proposals for CCA employing SHEDS-wood and other models should be welcomed.

    - Families are being asked to provide four (or five) urine samples and one tap water sample, fill out a questionnaire, and submit to five household visits likely less than 30 minutes in duration. Given this, a $150 incentive is quite high and may be viewed as coercive by an IRB.

    - The draft advertisements do not contain principal investigator and funding information. They would be of concern to some IRBs.

    - Compliance with the Health Insurance Portability and Accountability Act should be addressed.

    - A community representative on the IRB should be strongly considered.

- Field personnel should be required to pass an IRB-certified test of Ethical Treatment of Human Subjects prior to the beginning of the study.

- Since all of the study subjects are below the age of consent and likely below the age of assent, both their permission and the permission of their parents (not or as is stated) should be required prior to release of any information. Further, there should be specification of the intent to maintain confidentiality in removing identifiers.

- The statement regarding contacting the child's primary physician with questions is not sufficient. Most physicians would not be in a position to interpret the results. Any report to the participants and their parents should contain sufficient information, written in lay terms, which would allow the average parent to glean essential information. Simply telling them to go talk to their physician is not enough.

- There is a need to develop materials in Spanish to reflect the composition of the Albuquerque population. Further, with the potential for a large Native American and/or Latino/Latina populations, there may be need to develop culturally sensitive tools as well, and assure appropriate representation of people selected for study – which is difficult in a pilot/preliminary protocol.

- **Confounding Factors**
  - There is little provision for collection of data on potential confounding factors - diet, additional environmental exposures to As (pesticides in household and/or farm settings, golf communities, Chinese remedies, daycare environment), exposures to other chemicals/metals that are known to modify metabolisms (i.e., urinary levels) of As (e.g., selenium in dietary supplements, shampoos, photomaterials, etc.). Clear criteria or exclusion of subjects should be listed. Requirements of diary or urine collection (to be collected daily) may be too complex.
  - What is a typical diet in New Mexico? Is there likely to be little dietary intake of arsenic? If the diet includes rice e.g., arroz con pollo, arsenic exposure will be evident. What is the method of cooking? Is it likely to reduce or increase arsenic bioavailability? Such factors and activities should be assessed in developing a protocol.

  - Any concurrent, chronic or confounding diseases should be addressed and clear criteria for exclusion of subjects (if any) should be listed.

  - It is not clear how long a washout period is required to deplete As from tissues of individuals after a chronic exposure. The time period may be significantly longer than that proposed in the study. According to data in the protocol, three-phase elimination shows half-lives of 2 days (66% of As), 9.5 days (30%), and 38 days (3.7%). The protocol calls for a five-day washout. While there are 2.5 half-lives

for the 66% of the As following the fast washout metabolism, the other metabolic processes will only complete a fraction of one half life. Without developing a full pharmacokinetic model, one can estimate that after five days, these processes will leave $66\%*e^{-5/2\ln 2} + 30\%* e^{-5/9.5\ln 2} + 3.7\% e^{-5/38\ln 2} = 36\%$ of the original As body burden still in the body. This amount will continue to be reduced over time. However, if fish had been eaten at any time shortly before the beginning of the study, it will likely dominate the As body burden.

- **Analysis of As**
  - Multiple samples of tap and bottled water should be analyzed in the course of the study, unless assurance is provided that the concentration of As in the water system is reasonably stable. This was discussed in more detail previously under Design, Statistical and Quality Assurance Issues.

  - Analyzing total As in urines is likely insufficient. The Panel believed that detailed speciation data (including analysis of MMAV/III and DMAV/III if possible) would provide key information about the metabolism of As during exposures to CCA-wood along with important toxicological indications In 2001, the Panel was interested in high quality studies that are directed toward adding to the knowledge base and probabilistic assessment models under development at USEPA. This study is inadequate to comply with the 2001 "challenge". The "unwritten" concepts were more directed to "classical" research models of "peer review" and budgets to support the best proposals coming forward, and prioritized by a study section type of process. This is particularly important because metabolic profiles for As-Cr (Cu) complexes are unknown. Variations in yields and ratios of urinary metabolites may occur even if the total As levels do not change. It is reported that the analysis will be for "total hydride reducible arsenic," which includes inorganic As and MMA/DMA but not the arsenocholine, arsenobetaine, or other arsenosugars. This will allow control for possible sea food consumption by participants. More complete speciation would be of interest but requires a separation step, usually via HPLC, and is considerably more expensive. It may be useful to analyze for total As using an acid extraction followed by AFS, even HGAFS and compare with the HGAFS alone. The difference will give the arsenosugars, some of which may still be present in the early urine samples. Again, the extraction is relatively simple and can be done on a small aliquot of the urine.

  - The choice of analytical method is very important and should reflect the speciation requirements as well as expected relatively low levels of metabolites in urine. An analytical chemist should also be involved in the study planning from the very beginning to ensure that sample collection and storage is performed according to the analysis requirements.

  - Urine aliquots should be stored for additional analyses if later required.

- Evidence should be presented to support whether a difference of 4-5 µg/L can be detected by the analytical laboratory.

- More details of the analytical techniques outlined briefly in Sections 6.3.1.1-6.3.1.4 of the arsenic biomonitoring pilot study are warranted.

Minor Issues

- The metabolism of As is presented in a somewhat simplistic form (p.3 arsenic biomonitoring pilot study). In fact, it includes the following species: iAsV – iAsIII – MMAV – MMAIII – DMAV – DMAIII. All these metabolites are produced by human hepatocytes exposed to iAs and are found in urine of individuals exposed to iAs from drinking water. Some studies indicate that trimethylarsine oxide (TMAO) is also a metabolite of iAs in humans.

- The researchers should include at least a simple form of exposure monitoring. As an example, As analysis in swipes from children hands (as public commenter Dr. Helena Solo-Gabriel's [University of Miami] study suggests) after coming home from outside play should be considered. This does not have to be necessarily a thorough quantitative analysis; a semi-quantitative, yes/no type approach may be sufficient to confirm that the exposure to As actually occurred and would help greatly with data evaluation/interpretation.

- The selection of participants should reflect the ethnic and social variability of the population studied.

- While there are Chain of Custody forms for samples for urine, none are present for water samples. Further, such forms are only mentioned briefly and not at all addressed under the QA section.

- Two consecutive days (5 and 6, 17 and 18) are used to assess intraindividual day-to-day variability. However, the two samples are under different dietary regimes. This may be insufficient. Power calculations should be presented.

Question B. The Panel is asked to describe approaches for gathering additional data – e.g., data on the efficiency of transfer of surface residues to the skin surface (which has been identified as one of most critical model inputs based on the uncertainty analysis) – to improve the estimates of exposure and / or the level of confidence in such estimates, and with respect to these approaches, as well as the proposed pilot study, to comment on the cost of data generation, the amount of time to generate the data, and the degree to which the data will reduce uncertainty about the accuracy of the model estimates.

Should this study proceed, a number of changes need to be made to the questionnaires. The section on contact with home playsets and decks is not adequate to filter/stratify exposure to CCA since these may occur at municipal, day care, or other locations. In addition, the water and food consumption survey needs to be expanded to thoroughly cover sources of dietary arsenic, not just the standard fish items. Particularly since this study will be conducted in an area with large Mexican-American and Native American populations, an understanding of sources of dietary arsenic in ethnic diets is needed to assure that these exposures have been managed.

Issue 12. Prior to the availability of probabilistic models, such as SHEDS, OPP estimated the lifetime average daily dose (LADD) and corresponding cancer risk to pesticides via a deterministic approach using central tendency input parameters (median or mean values). Probabilistic models now allow OPP to express input parameters as distributions and subsequently generate a distribution of LADDs and corresponding pesticide cancer risks. In other words, the deterministic approach results in a single cancer risk value and the probabilistic approach results in a distribution of cancer risk values.

Question A. The Panel is requested to comment on whether in this probabilistic approach of using the upper bound arsenic cancer slope factor combined with using high-end LADDs would result in a significant overestimation of the risk for the more highly exposed percentiles of the population ? If this is an overestimate, what other values would the panel recommended using as replacements, or in addition to the values that were used that would minimize the overestimation of risk without substantially underestimating the risk for such percentiles.

In this assessment, the estimated risks are considered approximations because inaccuracies may occur when exposures are summed across routes at the quartile level especially in the upper percentile. This is due to the way the Monte Carlo simulations were conducted and the outputs summarized.

The Panel raised several questions concerning the issues presented. First, it is not appropriate to characterize the quoted arsenic cancer slope factor as an "upper bound." The arsenic cancer slope factor cited in the document is derived from a central estimate ED01 from an analysis of the data by Morales et al. (2000). Further work has since been done and published by Chen et al (2003a,b) and the National Research Council (2001). Thus, more recent work presented updated estimates of arsenic cancer risks from both Taiwanese and Chilean studies that appear to predict higher risks than the slope factor characterized as an "upper bound" in the question to the Panel. Although the current document alludes to a current Agency effort to consider the NRC estimates, it is not made completely clear to the reader in the executive summary that the result of adopting the NRC estimates would be to increase reported risk. In the spirit of the extensive sensitivity analysis performed by the Agency on the exposure estimates, the Panel believed it would be fair and appropriate for the Agency to at least disclose the magnitude and direction of change in the CCA risk estimates that would result from adoption of the revised NRC estimates and other technical considerations that are under current discussion within the Agency on arsenic and other cancer risks.

For example, in March, 2003, based on animal cancer bioassay observations, the Agency proposed a general conclusion that exposures of children under 2 years of age to mutagenic carcinogens should be considered to be ten times as potent per unit daily dose as comparable exposures for adults (and exposures of older children up to age 15 should similarly be considered to pose risks that are three times greater than analogous adult exposures). No direct explicit comparison of carcinogenic potency in younger vs. adult animals is currently possible based on data for inorganic arsenic itself. However the Panel wished to draw to the Agency's attention a recent positive bioassay finding of arsenic carcinogenesis in fetal animals (Waalkes et al. 2003).

This is in contrast to the extreme difficulty in inducing detectable excesses of cancers utilizing exposures of adult animals to inorganic arsenic. Further, although the human epidemiological studies that gave rise to the arsenic cancer slope factor estimates clearly included early life exposures, they also predominantly comprised adult exposures, unlike the solely early-life exposures estimated for the children covered in the SHEDS-Wood analysis. There is thus an issue of exactly how the proposed child-specific cancer risk assessment approach should be quantitatively applied to the SHEDS-Wood exposures, and what the foreseeable consequences of such application would be. The Panel suggested that revisions of the SHEDS-Wood risk analysis should explicitly address these topics. Finally, in addition to the lung and bladder cancer risks covered in the existing arsenic cancer slope factor, the Panel felt that risks of skin cancer from systemic arsenic exposures deserved mention and quantification.

The other passage in the question that the Panel found puzzling is the reference to "inaccuracies…(that) occur when exposures are summed across routes at the quartile level, especially in the upper percentile". The current exposure and risk analysis for CCA does not, to the Panel members' knowledge, incorporate any summing of exposures across routes at the quartile level, as suggested by the question. Instead, the SHEDS-Wood exposure assessment is an appropriate Monte Carlo analysis of overall exposures that would result from randomized combinations of estimated exposures from multiple routes from the detailed variability and uncertainty distributions derived and documented in the report of the SHEDS-Wood model methodology and results. Whenever random variables contribute to exposures from various routes and resulting risks, it is most appropriate to derive overall exposures and associated risks by such randomized draws from the variability and uncertainty distributions describing the causal mechanisms underlying the modeled processes. It would, of course, also be desirable to treat toxicological parameters such as the arsenic cancer slope factor in analogous probabilistic forms representing variability and uncertainty, as has been suggested elsewhere (Hattis et al., 2002, Hattis and Barlow, 1996). However until the Agency decides to implement such probabilistic analyses for cancer slope factors, RfDs, and RfCs, the best that can be done is to simply combine probabilistic exposure and dose analyses with the available single-point toxicological values.

Question B. The Panel is requested to comment on the range of percentiles, if any, at which there is a significant decrease in the reliability of the estimates of risk.

The technical aspects of this question are best addressed by multiple parallel simulation runs. The differences in percentile estimates among runs give the stability of the calculated values directly. Parallel runs should be standard practice in this kind of modeling. This having been said, in the two dimensional analyses where there are only 480 simulated individuals per uncertainty, it is likely that variability percentiles higher than the 99^{th} (based on only 5 individuals for each of the 180 uncertainty trials) are likely to be rather unstable.

However there is also an underlying policy question involved in the calculation and publication of specific percentiles in variability and uncertainty distributions. Higher percentiles are generally of risk management interest for variability rather than uncertainty (Hattis and Anderson, 1999), as is reflected in the greater number of variability vs. uncertainty iterations in the current SHEDS-Wood model approach. However members of this Panel, as technical

specialists, should not comment too overtly on exactly which information for which points on variability and uncertainty distributions are most salient for particular kinds of decision-making under the Agency's legislative mandates.

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