SAP Report No. 2000-03

PARTIAL REPORT

FIFRA Scientific Advisory Panel Meeting
September 27- 29, 2000
Held at the Sheraton Crystal City Hotel, Arlington, Virginia

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

Session III - Residential Exposure Models - REx

Session IV - Calendex™ Model

Session V - Aggregate and Cumulative Assessments Using LifeLine ™ - A Case Study Using Three Hypothetical Pesticides

NOTICE

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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 EPA 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 Larry Dorsey, SAP Executive Secretary, via e-mail at dorsey.larry@.epa.gov.

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REPORT:

FIFRA Scientific Advisory Panel Meeting
September 27, 2000, held at the Sheraton Crystal City Hotel, Arlington, Virginia

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

Residential Exposure Model - REx

Ms. Olga Odiott
Designated Federal Official
FIFRA/Scientific Advisory Panel
Date:_____

Ronald J. Kendall, Ph.D.
Chair
FIFRA/Scientific Advisory Panel
Date:_____

Federal Insecticide, Fungicide, and Rodenticide Act
Scientific Advisory Panel Meeting
September 27, 2000

SESSION III RESIDENTIAL EXPOSURE MODEL - REx

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PUBLIC COMMENTERS

Oral statements were made by:
None

Written statements were received from:
None

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 regarding Residential exposures- REx model. Advance notice of the meeting was published in the *Federal Register* on September 5, 2000. The review was conducted in an open Panel meeting held in Arlington, Virginia, on September 27, 2000. The meeting was chaired by Ronald J. Kendall, Ph.D. Ms. Olga Odiott served as the Designated Federal Official.

This session described the algorithms, input data requirements, and output reports associated with the Residential Exposure (REx) model. REx is a spreadsheet (EXCEL) based model which allows aggregation of multiple routes (dermal, inhalation, oral) and pathways (product use scenarios) to estimate exposure and risk from pesticides used in a residential setting. REx outputs are integrated into a cumulative risk assessment via the Calendex Model. EPA solicited SAP comments and peer review of the REx model (version 2.1G) and advice on how to proceed with future revisions of the model.

CHARGE

The specific issues to be addressed by the Panel are keyed to the background document, "Models - Residential Exposures - REx Model", dated September 5, 2000, and are presented as follows.

Question 1 Does the Panel consider the basic approach and concepts used in the REx model to be scientifically valid, complete and appropriate for estimating residential exposure and risk from multiple routes (oral, dermal, inhalation) and multiple residential-pathways?

Question 2 Does the Panel consider the screening-level and refined-level aggregate exposure construct used in REx appropriate for combining residential scenarios. What additional data are needed to determine co-occurrence of exposure during toxicologically relevant time periods?

Question 3 What recommendations does the Panel have regarding pre-assessment distributional analyses (stochastic inputs) and post-assessment uncertainty analyses that should be routinely addressed when using the “probabilistic mode”of REx?

Question 4 What key data gaps does the Panel recommend be addressed to support screening-level and refined residential exposure assessments conducted using REx? (e.g., children’s time-activity data; dermal exposure mass transfer studies, biomonitoring studies for comparison to model output, prioritization of pathways

to be routinely addressed based on exposure potential, micro- versus macro event exposure estimation)

Question 5 What should be routinely reported as part of REx modeling documentation (Good Exposure Assessment Practices)? (e.g., inputs and their sources, outputs - deterministic versus probabilistic)

SUMMARY OF PANEL RECOMMENDATIONS

The Panel noted that, in a broad sense, the REx model contains the elements that current scientific understanding dictates. However, since well characterized source-to-dose data sets are almost nonexistent and the individual components of the residential exposure model have only had limited calibration, the scientific validity of the model will remain questionable until more source-to-dose measurements are made.

Although the model includes lots of "multiples" (multiple exposure media, multiple pathway, multiple-route multiple-chemicals), these are not a guarantee of completeness. There is very limited treatment of uncertainty and variability at each stage of the model, and probabilistic distributions are only available for parameters that are well characterized. The Panel noted that parameters that are not well characterized are more likely to be uncertain and thus should be prime candidates for representation by distributions.

The Panel recommended that a mechanism be included for tracking mass balance of material available for exposure.

Because the software is modeled after the Agency's Draft Standard Operating Procedures (SOP's) for Residential Exposures Assessment, this document should be included in the REx documentation.

The Panel noted that there is a gross lack of available default input parameters for the model. The model use can be greatly enhanced with default parameters that are more pertinent to the exposure scenarios. Not having appropriate input parameters compromises the usefulness of the model. The Panel also noted that it would be useful to include in the REx documentation discussions pertaining to the context of default values when they are provided or used.

A member of the Panel recommended that the development of the model should have an overall plan for integration of its components. Without such a plan, the REx model becomes a fragmented collection of calculating algorithms that could unknowingly be misused. The Panel emphasized the importance of special studies to provide better scientific data on model inputs and multiple-exposure patterns and distributions.

In the work plan for REx, the task of "model uncertainty and model evaluation" is shown as one

of many concurrent model activities. But this diminishes the importance and value of the uncertainty analysis and model evaluation activities. The uncertainty analysis and model evaluation should be an overarching activity that wraps around all other aspects of model development.

The Panel noted that an important task for REx is the development of distributions for model inputs. This requires evaluation of available data and the application of sensitivity analyses, both local and global to the REx inputs.

A suggestion was made to model stochastic uncertainty with an exponential transform to better simulate the impact of extremes on the model results.

The Panel emphasized the importance of the technical quality of the stochastic inputs to the model calculations. Random number generators including those contained in Crystal Ball program should be documented and their quality assured.

A number of Panel members pointed to comparison of model predictions with biomonitoring data as the best test of overall performance of the model. There will be a need for iterative comparisons of biomonitoring data and model outputs.

The Panel noted that a better understanding of the temporal relationships that exist in real world uses of pesticides and the corresponding human exposures would benefit the refinement of the modeling effort.

The Panel encouraged extensive testing by users, in particular users removed from its development, since they are more likely to stress the model deficiencies and detect inconsistent results.

The Panel was of the opinion that, among other topics, the following should be explicitly addressed in the model documentation: a clear statement of what the model was designed to do, an overview of how the model works, the mathematical and statistical expressions employed in model calculations, and identification of chemicals and exposure scenarios for which the model should NOT be used.

Recommendations for tracking mechanisms were expressed for all three models under review in the SAP meeting on September 26 -29, 2000 (REx, Calendex™, and LifeLine™). For future evaluation of all models, the Panel requested that a group of case studies be presented that illustrate the linkage between the model output and personal exposure profiles. A list of computation equations with their respective parameters that would allow for step by step tracking of the exposure calculations should be included.

DETAILED RESPONSES TO THE CHARGE

Question 1 Does the Panel consider the basic approach and concepts used in the REx model to be scientifically valid, complete and appropriate for estimating residential exposure and risk from multiple routes (oral, dermal, inhalation) and multiple residential-pathways?

The Panel in its response addressed the separate concepts of scientific validity, completeness, and appropriateness of the REx model.

Scientific Validity

To this Panel the concept, "scientifically valid" implies that the model is supported by the science. However, the science of exposure assessment for pesticide residues is not mature and many of the processes and pathways addressed in REx are not well understood. Well characterized source-to-dose data sets that would provide empirical support if not a full scientific validation are almost nonexistent. The Panel notes that, in a broad sense, the REx model contains the elements that current scientific understanding dictates:

(I) Residue concentration on surfaces (lawns, floors, etc.) as a function of pesticide application.
(ii) Transfer of residues to skin surfaces
(iii) Dermal uptake of residues on skin
(iv) Ingestion uptake of residues on skin
(v) Oral ingestion of residues

The REx model is calibrated independently for each of these processes based on extant and relevant measurements. It is important to note that, although there is experimental observation to support model algorithms, the observations do not bracket the range of individual behaviors and application conditions that are likely in actual residential applications. Moreover, the individual components of the residential exposure model have had only limited calibration and have not been calibrated in concert. The scientific validity of the model will remain questionable until more source-to-dose measurements are made. Therefore it is necessary to consider the likelihood of surprise, that is, exposure pathways that have not been considered or properly quantified.

Completeness

The model certainly includes lots of "multiples" (multiple exposure media, multiple pathway, multiple-route multiple-chemicals), but these are not a guarantee of completeness. There are a number of limitations in the version reviewed by the Panel. It appears that the model has been set up to run only a one-day scenario. There is very limited treatment of uncertainty and variability at each stage of the model. Probabilistic distributions are only available for parameters that are well characterized. In a way this is contradictory to good modeling practice; parameters that are not well characterized are more likely to be uncertain and thus should be prime candidates for being

represented by distributions. Ongoing efforts on model evaluation are not strongly emphasized. There is a need to more carefully assess when to carry out deterministic versus stochastic assessments. There is a need to address neighborhood and regional scale aggregation of exposure. REx treats a household in isolation, but factors such as drift from one yard to another and pesticide exposures in residential areas near agricultural areas should also be included. There is a need to consider pesticide exposure during recreation activities (football, golf, soccer) in areas that have been treated with pesticides. REx lacks a mass balance model for the house or residence.

Appropriateness

Because of the uncertainties and continuing pace of change in the exposure field, it is appropriate and commendable that the model has the option for easily putting in alternative algorithms and input values. One advantage of the REx model is that the open and flexible form of the model makes it easy to use with validation studies using emerging biomarker data. Because of the uncertainty in the model and its inputs, it is appropriate that the model evaluation activities be made part of the development process for REx. As stated in the case study document for REx, professional judgement is used in developing many of the model algorithms. To many model developers, this is a code word for guesses. Although guesses are an essential component of model development, they need to be flagged and used as tools to set priorities for model improvement.

Members of the Panel noted that the REx model is primarily a calculation tool supported by many data inputs and assumptions that the user must control. It is difficult to comment on the model's scientific validity, or on the completeness and appropriateness of the basic approach and concepts without first commenting on how it could be used for the purpose for which it is designed.

The model represents a screening approach to residential exposures of pesticides. It contains a set of templates to explore scenarios described in the Agency's Draft Standard Operating Procedure (SOP's) for Residential Exposure Assessment. The model is in Excel spreadsheet format that allows wide flexibility to construct exposure scenario(s) and the aggregation of exposure from up to six scenarios. The model does not have the mechanism for estimating consecutive-day exposures, such that each subsequent day's exposure would have to be estimated in separate runs with its respective entry of parameters.

The spreadsheet format allows easy referencing of the computational procedures and easy extraction/exportation of information for further analysis or incorporation into a risk assessment document. The computational algorithms as listed in the Technical Guide are free of errors.

The appropriateness of the model for aggregate exposures and multiple residential scenarios is dependent on how the parameters were estimated or used as model input. It is recommended that a mechanism be included for tracking mass balance of material available for exposure. One specific area is to eliminate "double counting." The total amount available for exposure through

more than one route should not exceed the total amount of chemical present in the exposure media. For example, the amount that is taken up via hand-to-mouth action (Ingestion # 110), should not also be available for dermal uptake (Dermal # 105/106). Another example is in estimating the amount available from fluxes of impregnated material. The concentration at the surface available to exposure during a time period would not just be the amount newly dissipated (e.g., with a lower flux rate for a subsequent day) but also the amount dissipated from the previous time period that has not been transferred to an individual's skin or clothing.

The documentation and references included in the software were very helpful. Because the software is modeled after the Residential Exposures Assessment SOP, this document should also be included in the REx documentation.

The default parameters used in the case study reflect a gross lack of available default input parameters for the model. This is probably the most dissatisfying area of the model application. For example, in the case study, the transfer factor derived from jazzercise studies after indoor fogger application was used as surrogate data for estimating exposures through lawn care application. The availability of more pertinent data should be explored. The model use can be greatly enhanced with default parameters that are more pertinent to the exposure scenarios (e.g., transfer factor for specific contact surfaces, unit exposures for different application methods, dermal absorption factors for specific chemicals). Not having appropriate input parameters compromises the usefulness of the model.

In the case of transfer factors from carpets, it is also noted that, the total amount of exposure per person in 18 minutes jazzercise would equal the amount of transferable residue from more than 6.5 m^2 carpet area. It would appear that a stated room size of 21 m^2 would be completely depleted of residue after 18 minutes of jazzercise by 4 persons. Thus, it would be useful to include in the REx documentation discussions pertaining to the context of default values when they are provided or used.

Question 2 Does the Panel consider the screening-level and refined-level aggregate exposure construct used in REx appropriate for combining residential scenarios. What additional data are needed to determine co-occurrence of exposure during toxicologically relevant time periods?

The capability of the REx user to conduct both deterministic, often conservative, screening assessments and more detailed stochastic simulations of aggregate exposures and dosages is a defining feature of the residential exposure model. The “macro” level features enable users to evaluate maximal exposures under generic parameters derived from prior research studies and testing and evaluate the relative magnitude of exposures by source and mechanism for adults and children. The "micro" feature enables the user to supply alternative parameter values or to simulate exposures over the range of parameter values found in prior research and testing studies. Distributional simulation of parameters is implemented for pulmonary absorption (triangular),

dermal absorption (uniform), oral absorption (triangular), and body weight (lognormal). User inputs can be modified for application dates, rates, transfer factors, clothing coverages, and other factors. The value of the REx model lies in its relatively simple structure for defining and estimating aggregate residential exposure for individual children and adults for toxicologically relevant time periods.

The Panel noted in response to this question that, given the time and guidance provided to the Panel to examine the model, it is difficult to tell what gaps there are or where a more detailed model is needed. A member of the Panel noted that the development of the model should have an overall plan for integration of its components. Without such a plan, the REx model becomes a fragmented collection of calculating algorithms that could unknowingly be misused. The REx model can never be fully validated; however, the Panel members in their response to this question emphasized the importance of special studies to provide better scientific data on model inputs and multiple-exposure patterns and distributions.

Question 3 What recommendations does the Panel have regarding pre-assessment distributional analyses (stochastic inputs) and post-assessment uncertainty analyses that should be routinely addressed when using the "probabilistic mode"of REx?

An important use of models in addition to making predictions is to identify dominant sources of uncertainty. It is important to judge a model with regards to this goal. In considering the layout of REx, the model developers have shown the task of "model uncertainty and model evaluation" as one of many model components. Thinking of this task as one of many concurrent model activities diminishes the importance and value of the uncertainty/evaluation activities. The big picture should have uncertainty analysis and model evaluation as an overarching activity that wraps around all other aspects of model development. In addition to model evaluation, it is important to include data evaluation in the model development and application. An important task for REx is the development of distributions for model inputs. This requires an evaluation of available data and an evaluation of how sensitive the model outcome (location and spread of values) is to the location, shape, and spread of the various inputs. There is a need to propose and apply both local and global sensitivity analyses to the REx inputs.

These analyses are very important for two reasons:
(1) they make it possible to predict extremes of exposure
(2) they help to predict the range of values to be expected in biomonitoring studies. Without knowing the range of values, it will be impossible to assess the agreement between the model and biomonitoring data.

One member of the Panel suggested that REx should allow the user to focus more carefully on the extreme tail of the exposure distribution. A suggestion was made to model stochastic uncertainty with an exponential transform to better simulate the impact of extremes on the model results.

The Panel emphasized the importance of the technical quality of the stochastic inputs to the model calculations. It is important that the random number generators, including those contained in the Crystal Ball program, be documented and their quality assured.

Question 4 What key data gaps does the Panel recommend be addressed to support screening-level and refined residential exposure assessments conducted using REx? (e.g., children's time-activity data; dermal exposure mass transfer studies, biomonitoring studies for comparison to model output, prioritization of pathways to be routinely addressed based on exposure potential, micro- versus macro event exposure estimation)

There are many areas where data on distributions and processes are needed if REx is to be used effectively to simulate real world exposures. The most important data gap is the lack of data that can be used to evaluate ultimate model performance. A number of Panel members pointed to comparison of model predictions with biomonitoring data as the best test of overall performance of the model. There is certainly a need for biomonitoring data, but more importantly, there is a need to think about how biomonitoring data can be used to evaluate REx. (Could we be getting the right answer for the wrong reason?) There will be a need for iterative comparisons of biomonitoring data and model outputs. This will require posing questions about whether the model predictions are within the confidence interval predicted for the model and assigned to the monitoring values.

The Panel noted specific areas where added data would benefit the refinement of the modeling effort. Obviously, in addition to the biomonitoring data, data are needed to improve understanding of the specific exposure pathways and transfers with the greatest contribution to the high level of uncertainty in applying the model. Immediate benefit would probably lie in better understanding temporal relationships that exist in real world uses of pesticides and the corresponding human exposures: co-occurring uses, human activity patterns, frequency of uses, time functions in transfer factors, decay/dissipation of applied substances.

The need for better input data and better understanding of the modeled processes can often best be refined through feedback from knowledgeable users. The Panel encourages extensive testing by users, in particular testing by users removed from its development is important, as they are more likely to stress the model deficiencies and detect inconsistent results.

Question 5 What should be routinely reported as part of REx modeling documentation (Good Exposure Assessment Practices)? (e.g., inputs and their sources, outputs - deterministic versus probabilistic)

The Panel noted that the following topics should be explicitly addressed in the model documentation:

(I) A clear statement of what the model was designed to do.
(ii) An overview of how the model works--use a very simple chart showing the source-to-dose pathways.
(iii) The mathematical and statistical expressions employed in model calculations, including those that are part of the operating system or provided with the programming language as well as those programmed by the developers.
(iv) Identification of chemicals for which the model is not suited and explain exposure scenarios and chemicals for which the model should NOT be used.

Other specific comments by the Panel on the REx documentation include the following. Page 4 of the Technical Guide provides a good list of model input parameters. For each parameter, it is good to reference its source (e.g., default from the Pesticide Handler Exposure Database (PHED), literature publication). When a deterministic value is used, the documentation should provide the reference point in a distribution (e.g., mean, median, percentile). When the distribution is used for a parameter, provide the summary data (e.g., distribution type, mean, range). When surrogate data are used, provide the scenario of the surrogate (e.g., using transfer factor from carpet as surrogate for turf transferring).

The output worksheet contains good information for the model output. However, a couple of entries in the output spreadsheets may appear to be misleading. One is the appearance of having an exposure equation containing a multiplier of zero (e.g., for Ingestion 102, the entry for the multiplier "t" is zero). The other potentially misleading expression is an entry for the total exposure from multiple routes when the aggregate "exposure" should have been based on dose. The scenario-specific output should indicate the exposure, dose, and margin of exposure (MOE) from each route.

SAP Report No. 2000-03-B
MM/DD/YY

REPORT:

FIFRA Scientific Advisory Panel Meeting
September 28, 2000, held at the Sheraton Crystal City Hotel, Arlington, Virginia

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

Calendex ™ Model

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Designated Federal Official
FIFRA/Scientific Advisory Panel
Date:_____

Ronald J. Kendall, Ph.D.
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Date:_____

Federal Insecticide, Fungicide, and Rodenticide Act
Scientific Advisory Panel Meeting
September 28, 2000

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PUBLIC COMMENTERS

Oral statements were made by:
None

Written statements were received from:
None

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 regarding Calendex™ model. Advance notice of the meeting was published in the *Federal Register* on September 5, 2000. The review was conducted in an open Panel meeting held in Arlington, Virginia, on September 28, 2000. The meeting was chaired by Ronald J. Kendall, Ph.D. Ms. Olga Odiott served as the Designated Federal Official.

A requirement of the Food Quality Protection Act is that exposures to pesticides across various pathways and routes (e.g., dermal exposure through turf uses) be appropriately combined such that an "aggregate" exposure assessment can be performed. The Agency currently uses Calendex™ software from Novigen Sciences to perform this aggregation. Calendex™ permits a time-based integration of both residential and dietary (food and water) exposures to pesticides. This session described the components and methodologies used by the Calendex software, the basic concepts and assumptions behind Calendex™, and its algorithms and procedures.

CHARGE

The specific issues to be addressed by the Panel are keyed to the background document, "Models-A Consultation on the Calendex™ Aggregate Exposure Model", dated September 1, 2000, and are presented as follows.

Question 1 Does Calendex appropriately combine (or aggregate) exposures to pesticides in a way which adequately incorporates important factors associated with multiple routes of exposures, including the probability of co-incident applications and/or exposures and the temporo-spatial aspects of exposure?

Question 2 Given the absence of longitudinal data concerning food consumption, is the method by which Calendex incorporates and uses the available 1-day consumption data from USDA's Continuing Survey of Food Intakes by Individuals (CSFII) reasonable? Are there any suggestions or improvements that Panel members recommend?

Question 3 Calendex offers the potential for overlaying daily exposure through multiple scenarios. Since the Calendex software does not limit the user to specific pre-programmed or "canned" exposure scenarios, the program allows the user to incorporate any exposure scenarios that can be conceived of, created, and modeled by the user. Are there any reasonable situations for which OPP can limit the number of scenarios considered or can otherwise limit the analysis to those scenarios which are considered non-negligible in terms of exposure? What criteria should be considered to exclude a particular scenario?

Question 4 Does that Panel see any difficulties in using input data expressed as both point estimates and distribution estimates in the same (single) exposure analysis? Are there any cautions the Panel may offer to OPP with respect to interpretation of results or performance of sensitivity analyses when inputs into an assessment are present as both point estimates and distributional estimates?

Question 5 Consistent with previous SAP advice, OPP has elected to use the "Total MOE approach" in the conduct of its aggregate risk assessment and Calendex has adopted this methodology when performing aggregate risk assessments. Does the SAP have any further cautionary notes or comments on this approach?

Question 6 OPP in its initial evaluation of potential residential exposures conducts its assessments assuming that use occurs, i.e., OPP estimates exposures given the assumption of use as per maximum label directions. When performing aggregate exposure assessments in which food, water, and residential exposures are combined, OPP intends to incorporate the probability of treatment in its assessments to account for co-occurrence. If this information is available, OPP would also intend to probabilistically incorporate the range of application rates in its assessments (this handling of data is similar to that used for food where actual percent crop treated and range of application rates is fully incorporated into the probabilistic assessment) Does the SAP have any comments, suggestions, or thoughts on this approach?

SUMMARY OF PANEL RECOMMENDATIONS

The Panel concluded that at this stage of the Calendex™ model development, and based on the information provided to the Panel, they could not verify, refute, or validate Calendex™.

The Panel noted the need for a mechanism to track the Calendex™ computation and increase user confidence in its output. The Panel suggested two approaches for accomplishing this task: 1) instead of simply presenting curves of exposure values, select a point on a curve, evaluate how it came about, present the result using a narrative, and support the narrative with a set of calculations that allow the reader to track how the cumulative exposure values came about, and 2) demonstrate the use of Calendex™ with a group of scenario-based case studies that cover a range of an individual's exposure and personal profiles, capturing the demographic, geographic, and temporal variations and characteristics.

Similar recommendations for tracking mechanisms were expressed for all three models under review in the SAP meeting on September 26-29, 2000 (REx, Calendex™, and LifeLine™ models). The Panel requested that for future evaluation of these models, a group of case studies that illustrate the linkage between the model output and personal exposure profiles be provided.

The Panel stated that in the absence of longitudinal data concerning food consumption, not much can be said about correlation. Longitudinal studies of food consumption, coupled with biomonitoring for pesticide consumption, would help determine if the correlations are sufficiently high that they would need to be included in the model.

Regardless of the length of exposure simulation, Calendex™ uses an individual's Continuing Survey of Food Intakes by Individuals (CSFII) record. The Panel stated that this may be justifiable for a few days of exposure, but modeling an individual's dietary exposure for a prolonged period of time based on 1-3 days food consumption records would constitute a gross extrapolation of the consumption data and disregard of the variations and changes in dietary patterns over time.

The daily dietary records provided by CSFII provide one-day sample snapshots of individual food consumption. Aggregated over the population sample, these data provide sample estimates of population-averaged daily consumption and seasonal/geographic trends; however, these data do not capture autocorrelation (positive or negative) in individual eating behaviors.

Imputation of food consumption over time is developed through random draws from individually reported daily patterns in theUSDA CSFII. This restricts variability and does not capture seasonal or other effects. To better reflect variability in individual diets over time and seasons, Calendex might match CSFII respondents to other similar individuals in the CSFII data and draw from the collected set of daily reports of consumed foods as a basis for imputing daily residues for simulation studies that cumulate exposures over time.

The Panel also suggested use of the full CSFII data set, converting the daily reports of food consumption to residue exposures for the active ingredients of interest. The distribution of residues from the DEEM™ model could then be modeled to capture the population average exposures for individuals as a function of time and individual characteristics as well as the individual exposures about the population averaged values.

The Panel noted that it is not desirable for a software to reject conducting simulations when the user enters a reasonable set of input parameters. Testing a model with some extreme scenarios often facilitates understanding of how the model functions.

Point estimates for model parameters should be limited to fixed conversion factors and stated factors (i.e., application rates) in the model. In lieu of any real data driven evidence, narrowly bounded uniform or other symmetric distributions about the point value would be a step toward reflecting the true variability in the simulation exercise.

The overall consideration when aggregating exposures from multiple routes is to ensure that the basis for addition is the uptake "dose" and not merely the amount of contact. Thus, the assumptions used to aggregate among the exposure routes should be clearly stated and the uncertainties and sensitivity of the total margin of exposure (MOE) to any uptake assumptions

should be clearly articulated.

The Panel noted that incorporating the probability of treatment will increase the flexibility of Calendex™ for addressing aggregate and cumulative exposures, but it could also decrease the overall reliability of the model results in situations where the probability of application is not well characterized. A group of case studies as recommended in response to Question 1 would be useful for identifying some of the more obvious points of consideration in the use of input data.

DETAILED RESPONSES TO THE CHARGE

Question 1 Does Calendex™ appropriately combine (or aggregate) exposures to pesticides in a way which adequately incorporates important factors associated with multiple routes of exposures, including the probability of co-incident applications and/or exposures and the temporo-spatial aspects of exposure?

The Panel considered this a very open-ended question. It appears that the Panel is being asked to confirm whether this model is correct--an almost impossible task. In reality it could take months to confirm how well this model works. Because the Panel cannot really verify, refute, or validate this model, it is not possible to confirm the correctness of the model, but it is possible to offer advice on how to build confidence in these sorts of models. The ultimate test of these models is whether the Agency can build confidence in the model and its use.

At this time, the Panel is in no position to make a detailed validation of the many models and assumptions in Calendex™. Overall, the model allows the user to specify the scenarios of exposure based on the knowledge of pesticide use (e.g., frequency, level). How well the exposure estimation reflects the real life situation is dependent on the model construction as well as the user's knowledge on pesticide use patterns, both temporally and spatially. Some routes may be fairly predictable (e.g., application of a domestic pesticide indoors), while others will never be certain (e.g., the long route from application of a pesticide on a farm, through transportation, storage, and preparation to ultimate consumption). Thus, Calendex™ will always be limited by the capacity to describe every possibility. One can make the predictions more conservative by running Calendex™ with exaggerated levels of variability. This will push up the mean level of exposure and also raise the high percentiles.

Calendex™ operates on a residential scale in space and can accumulate exposures in time. To do this it has an extensive set of scenarios. However, restricting the model to a residential scale does not provide an aggregation of exposures at different spatial scales. In this sense it may be missing some important scenarios, such as neighborhood scale exposures and exposures of agricultural communities.

The complexity of the model for aggregate exposures and the many input parameters with their distributions point to the need for some tracking mechanism to provide a context for the output. The Panel suggested two approaches to track the Calendex™ computation and increase user confidence in its output:

- Instead of presenting curves of exposure values, select a point on a curve and evaluate how it came about. Present the result using a narrative and support the narrative with a set of calculations that allow the reader to track how the cumulative exposure values came about. This is similar to the Critical Exposure Commodity (CEC) analysis included in the Dietary Exposure Evaluation Model (DEEM™) developed by the same company (Novigen) and shares the same consumption databases used in Calendex™. The model-generated CEC file provides the exposure profile and commodity contributions of the high-end exposure individuals.

- Demonstrate the use of Calendex™ with a group of scenario-based case studies that cover a range of an individual's exposure and personal profiles, capturing the demographic, geographic, and temporal variations and characteristics. For example, would the day of high exposure for an individual be likely on a day of lawn treatment, or would the high exposure be an aggregate from multiple pathways all with substantial contributions? What would be the exposure when the lawn treatment was at the highest rate and the individual has eaten one frequently consumed commodity at or near the tolerance when such combination is possible? Did the combination correspond to any particular activity and eating patterns?

Similar recommendations for tracking mechanisms are expressed for all three models under review in the SAP meeting on September 27-28, 2000 (REx™ model, Calendex™, and LifeLine™). For future evaluation of all models, the Panel requests that a group of case studies be presented that illustrate the linkage between the model output and personal exposure profiles. A list of computation equations with their respective parameters that would allow for step by step tracking of the exposure calculations should be included.

Question 2 Given the absence of longitudinal data concerning food consumption, is the method by which Calendex incorporates and uses the available 1-day consumption data from USDA's CSFII reasonable? Are there any suggestions or improvements that Panel members recommend?

Calendex™ uses one-day consumption data and assumes independence between days. If Calendex™ is applied over a long enough time, or with enough replications of random scenarios, it should give the correct mean aggregate exposure. If in reality there is positive correlation between days, then Calendex™ will overestimate the variance in exposure; if in reality there is negative correlation, Calendex™ will underestimate the variance in exposure.

In the absence of longitudinal data, not much can be said about correlation. Correlation between

days will result from many factors including meal planning cycles, availability of local produce, and cultural tradition. If a household gets a basket of blueberries and eats it over several days, the correlation will be positive. If they don't have a salad today because they had one yesterday, the correlation will be negative.

Ultimately, it is correlation between daily pesticide intake that matters; correlation between food consumption on successive days is of less interest. Longitudinal studies of food consumption, coupled with biomonitoring for pesticide consumption would help determine if the correlations are sufficiently high that they would need to be included in the model.

Further comments were given to the specific use of the available consumption data. It appears the rich data in food consumption pattern was not utilized in Calendex™ because of the emphasis on modeling the exposure of "individuals". Regardless of the length of exposure simulation, Calendex™ uses an individual's CSFII record. While this may be justifiable for a few days of exposure, modeling an individual's dietary exposure for a prolonged period of time (e.g., subchronic or seasonal, annual) based on 1-3 days food consumption records would be a gross extrapolation of the consumption data and disregard of the variations and changes in dietary patterns over time. Recognizing the lack of longitudinal food consumption data, the Panel recommended the following considerations for using the entire CSFII data:

> Population representation of daily food consumption patterns over time is a function of seasonal and geographic effects, individual preferences for food types and amounts and correlation in individual eating patterns over time. The daily diary records provided by CSFII provide one-day sample snap-shots of individual food consumption. Aggregated over the population sample, the data provide sample estimates of population-averaged daily consumption and seasonal/geographic trends; however, these estimates do not capture autocorrelation (positive or negative) in individual eating behaviors. Individual behaviors for food consumption can deviate significantly from population averaged profiles.
>
> Ideally, Calendex™ simulations for individuals would impute a sequence of daily food consumption profiles that reflect a random sampling of individual consumption profiles over the full period. This is not possible given existing data or even practically feasible to develop for periods exceeding a week or more.
>
> Imputation of food consumption over time is now developed through random draws from individually reported daily patterns in USDA CSFII. For each CSFII respondent, the Calendex simulation stochastically generates up to 5000 residue values for the food servings reported by respondents for each day of fixed three day periods (CSFII 1989-1991) or two day periods (CSFII 1994-1996). Residues are therefore allowed to vary stochastically; however, the pattern of consumed foods that underlie the residue distribution does not vary substantially for individual subjects over time. In short, Calendex assumes that each individual has at most two or three versions of their daily diet.

To better reflect variability in individual diets over time and seasons, Calendex might match CSFII respondents to other similar individuals in the CSFII data and draw from the collected set of daily reports of consumed foods as a basis for imputing daily residues for simulation studies that cumulate exposures over time. For example, assuming that CSFII provides 50 daily food consumption breakdowns for 20 males age 20-24 who live in the West Region, a Calendex simulation would use the characteristics of each of these 20 individuals in a cumulative exposure. Instead of repeatedly using only their personal one day reports of foods consumed to simulate dietary exposures for each of these individuals over long periods of time, Calendex could draw from the set of one day reports for persons in their group. The added variability in the simulated daily diet and the corresponding variability in the associated residue simulation would permit Calendex to better reflect real world variability in day to day and cumulative dietary exposures.

A second and possibly preferred alternative is to use the full CSFII data set, converting the daily reports of food consumption to residue exposures for the active ingredients of interest. The distribution of residues from the DEEM™ model could then be modeled to capture the population average exposures for individuals as a function of time and individual characteristics as well as the individual exposures about the population averaged values. If sufficient samples are available with multiple CSFII daily food consumption reports, it may be possible to examine individual autocorrelations over time. The imputation of daily exposures would then be based on the estimated model with each draw including a time/subject dependent residual from the modeled distribution. If data on short term autocorrelation were available they could be incorporated into draws for sequences of days.

Question 3 **Calendex offers the potential for overlaying daily exposure through multiple scenarios. Since the Calendex software does not limit the user to specific pre-programmed or "canned" exposure scenarios, the program allows the user to incorporate any exposure scenarios that can be conceived of, created, and modeled by the user. Are there any reasonable situations for which OPP can limit the number of scenarios considered or can otherwise limit the analysis to those scenarios which are considered non-negligible in terms of exposure? What criteria should be considered to exclude a particular scenario?**

In general, it is not desirable for a software to reject conducting simulations when the user enters a reasonable set of input parameters. Often it is the extreme scenarios that help to understand the model. It is usually worthwhile to begin testing or validation of a model with some extreme scenarios and see if the output makes sense, as this will facilitate understanding of how the model functions.

Question 4 **Does that Panel see any difficulties in using input data expressed as both point estimates and distribution estimates in the same (single) exposure**

analysis? Are there any cautions the Panel may offer to OPP with respect to interpretation of results or performance of sensitivity analyses when inputs into an assessment are present as both point estimates and distributional estimates?

The use of point estimates in model simulation attenuates the variance of simulation results and, in cases of serious misrepresentation of central tendency or correlated parameters, could bias the results (the correlation of a variable parameter in a point value is implicitly zero). Point estimates for model parameters should be limited to fixed conversion factors and stated factors (i.e., application rates) in the model. Clearly, empirical and other data do not exist for all of the variable parameters in the model. If the point values are measures of central tendency or even "best guesses", the simulation would benefit from introducing draws from distributions, even if it were a non-informative prior (e.g., uniform distribution) for that parameter. In Calendex™, users should be encouraged by the program to think about and supply distributional forms and parameters. In lieu of any real data-driven evidence, narrowly bounded uniform or other symmetric distributions about the point value would be a step toward reflecting the true variability in the simulation exercise.

When testing marginal and conditional effects of particular pathways or parameter assumptions in the model, it is important that program users have the ability to quickly fix other parameters at specified values—either expected values from distributions or user supplied point values.

Question 5 Consistent with previous SAP advice, OPP has elected to use the "Total MOE approach" in the conduct of its aggregate risk assessment and Calendex has adopted this methodology when performing aggregate risk assessments. Does the SAP have any further cautionary notes or comments on this approach?

One issue with respect to the "total MOE approach" is to calculate or aggregate exposure by route and maintain these exposures independently by route--that is to allow the user to always be able to see the aggregated exposure by route. However, in addition to this feature, which is likely already in the Calendex™ system, it would be helpful for the user to have the ability to track all the exposure pathways that contribute to aggregate exposure for each exposure route. Another issue is the aggregation of exposures across routes. This requires a PBPK model, and the aggregation across routes will be very sensitive to the PBPK model used. Thus, the assumptions used to aggregate among the exposure routes should be clearly stated, and the uncertainties and sensitivity of the total MOE to any uptake assumptions should be clearly articulated.

The overall consideration when aggregating the "exposure" from multiple routes is to ensure that the basis for addition is the uptake "dose" and not merely the amount of contact (i.e., the "exposure").

Question 6 **OPP in its initial evaluation of potential residential exposures conducts its assessments assuming that use occurs, i.e., OPP estimates exposures given the assumption of use as per maximum label directions. When performing aggregate exposure assessments in which food, water, and residential exposures are combined, OPP intends to incorporate the probability of treatment in its assessments to account for co-occurrence. If this information is available, OPP would also intend to probabilistically incorporate the range of application rates in its assessments (this handling of data is similar to that used for food where actual percent crop treated and range of application rates is fully incorporated into the probabilistic assessment) Does the SAP have any comments, suggestions, or thoughts on this approach?**

Incorporating the probability of treatment will increase the flexibility of Calendex™ for addressing aggregate and cumulative exposures to various pesticides. It offers the potential for making the model more fully stochastic. Nevertheless, adding probability of treatment to the model will tend to decrease the overall reliability of the model resulting in situations where the probability of application is not well-characterized. There is a need to balance the gain in realism with any potential loss of reliability that derives from adding a process that remains uncertain or for which the variability is not well characterized--particularly at the high end of the probability distribution. The Panel is hopeful that a group of case studies as recommended under Question 1 would be useful for identifying some of the more obvious points of considerations in the use of input data.

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REPORT:

FIFRA Scientific Advisory Panel Meeting September 28, 2000, held at the Sheraton Crystal City Hotel, Arlington, Virginia

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

Aggregate and Cumulative Assessments Using LifeLine ™ - A Case Study Using Three Hypothetical Pesticides

Ms. Olga Odiott
Designated Federal Official
FIFRA/Scientific Advisory Panel
Date:_____

Ronald J. Kendall, Ph.D.
Chair
FIFRA/Scientific Advisory Panel
Date:_____

Federal Insecticide, Fungicide, and Rodenticide Act
Scientific Advisory Panel Meeting
September 28, 2000

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PUBLIC COMMENTERS

Oral statements were made by:
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Written statements were received from:
None

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 regarding aggregate and cumulative assessments using LifeLine™. Advance notice of the meeting was published in the *Federal Register* on September 5, 2000. The review was conducted in an open Panel meeting held in Arlington, Virginia, on September 28, 2000. The meeting was chaired by Ronald J. Kendall, Ph.D. Ms. Olga Odiott served as the Designated Federal Official.

The purpose of this presentation was to describe an analysis of aggregate exposures and risks associated with exposures to a hypothetical pesticide, Alpha, and the cumulative exposure to and risk from three hypothetical pesticides, Alpha, Beta, and Gamma. The cumulative risks were evaluated by determining the systemic (absorbed) doses that result from inhalation, dermal, and oral exposures to the pesticides. A "toxicity equivalent" model of cumulative risk was used to quantitatively evaluate cumulative risks. Assessments were performed using LifeLine™ Version 1.0. This model simulates pesticide exposure using an individual-based approach where daily exposures are evaluated for each person, season, and location. The presentation focused on LifeLine™ architecture and application options in conducting aggregate and cumulative exposure/risk assessments. The Panel was asked to comment on future applications of LifeLine™ and to provide guidance on how best to interpret output reports derived from the model.

CHARGE

The specific issues to be addressed by the Panel are keyed to the background document, "Models - Aggregated Cumulative Assessments using LifeLine™ ," dated September 5, 2000, and are presented as follows.

1. Model design

Question 1.1 Does the framework of LifeLine™ provide the appropriate definitions (temporal, spatial and demographic) on which to overlay exposure details? And do the model's outputs allow sufficient flexibility for understanding the exposure/risk profiles?

Question 1.2 Does LifeLine™ provide the necessary elements of analysis for performing aggregate and cumulative risk assessments? And for delineating age-related exposure opportunities and risk?

2. Case study using LifeLine™

Question 2.1 Age-related exposure profiles are vital components of a risk assessment. The periods of high exposure and the contributors to that exposure are necessary elements of a risk assessment model. Does the panel agree that the demonstration case is a reasonable scenario and that children's exposures can be higher than

adults' due to higher dietary intake on a weight basis and higher frequency of hand to mouth exposure events?

Question 2.2 Understanding the source and route of exposure are key elements to aggregate and cumulative exposure assessments. Does the case study demonstrate that when sources of pesticides are independent, aggregate exposure can tend to be dominated by a single route of exposure at given periods of time?

Question 2.3 Does the panel agree that this paper demonstrates that probabilistic models using existing data can characterize both cumulative and aggregate exposure to pesticides? And that the LifeLine™ model can be used to identify the critical sources of exposure and the influence of factors such as age and season?

SUMMARY OF PANEL RECOMMENDATIONS

While the presentation provided an interesting overview of LifeLine™ 's capabilities, the Panel would require a much more detailed look at LifeLine™ before it could attest to its validity.

The framework of LifeLine™ provides for a long-term aggregation of exposure to individuals; it is not well-suited to short-term exposure events. LifeLine™'s ability to track a calculation back to those factors that contribute to the magnitude of exposure is useful and important.

The Panel was of the opinion that a significant disadvantage of LifeLine™ is that the model is not currently set up to calculate pooled exposures across a population or cutting the population different ways.

The Panel emphasized the importance for the LifeLine™ model to provide explicit treatment of uncertainty. There is little consideration of the severe limitation placed on the model by the lack of a single reliable data set on longitudinal lifetime activity patterns.

The Panel was of the opinion that the model contains more than a necessary number of elements. Including unnecessary elements makes the model more complex than needed, more difficult to use and to understand, and increases the opportunity for error (in data entry, etc.)

The Panel agreed that LifeLine™'s ability to report the contribution of individual sources to the total exposure measurement is valuable.

The Panel found the questions related to the case study very difficult to respond to. The questions hint at a request for professional judgement on the plausibility of a result that is based on a model simulation with little empirical basis for evaluation or testing. The Panel requested

that its responses be interpreted in this light and not be construed as a scientific endorsement of the findings or relationships implied by the case study simulation.

The Panel agreed that LifeLine™ can be used to identify critical sources of exposure and patterns over age and seasonal periods, but this strength should not be construed to mean that LifeLine™ provides a scientifically valid profile of *all* sources and processes that contribute to seasonal and age-specific patterns in aggregate and cumulative exposures.

The Panel was firm in its opinion that, in the future, it would be best served by the ability to closely examine and test a working version of the LifeLine software and to have the opportunity to review an analysis of the uncertainty that is inherent in LifeLine's model-based estimates of aggregate and cumulative exposure.

DETAILED RESPONSES TO THE CHARGE

1. Model design

Question 1.1 Does the framework of LifeLine™ provide the appropriate definitions (temporal, spatial and demographic) on which to overlay exposure details? And does the model's outputs allow sufficient flexibility for understanding the exposure/risk profiles?

The focus of this question is quite narrow and does not direct the panel to consider the accuracy, appropriateness, and utility of the LifeLine™ model itself. The framework of LifeLine™ provides for a long-term aggregation of exposure to individuals. Thus, the model is not well suited to short-term exposure events. The outputs allow flexibility but may have some limitations with regard to pooling spatial and demographic groups. LifeLine's audit tracking of exposures is a particularly valuable feature. The ability to track a calculation back to those factors that contribute to the magnitude of exposure is useful and important. In addition, the graphical displays are informative and useful. It appears to be outside of the scope of this model, but it is a significant disadvantage that the model is not currently set up to calculate a pooled exposure across a population or cutting the population different ways, i.e., to calculate the 1-yr per caput dose within a specified demographic group (i.e., a city, a county, or an ethnic group).

Question 1.2 Does LifeLine™ provide the necessary elements of analysis for performing aggregate and cumulative risk assessments? And for delineating age-related exposure opportunities and risk?

Because risk involves uncertain consequences, it is important that a model such as LifeLine™ provide explicit treatment of uncertainty. LifeLine™ is well constructed for addressing variability, but it lacks an explicit treatment of uncertainty. Another issue is aggregation over both space and time. LifeLine™ does very detailed and long-term aggregation of exposures over time, but it

does not appear to aggregate over spatial scales, such as neighborhood-scale exposures or community scale (in particularly agricultural communities). There is little consideration of the severe limitation placed on the model by the lack of a single reliable data set on longitudinal lifetime activity patterns. No single database includes this information and so it must be constructed from multiple data sets. What is the uncertainty added by this construct?

An adjunct issue is whether the model contains more than a necessary number of elements. Including unnecessary elements makes the model more complex than needed, more difficult to use, more difficult to understand, and increases the opportunity for error (in data entry etc.)

The Panel noted that LifeLine™'s ability to report the contribution of individual sources to the total exposure measurement is valuable.

2. Case study using LifeLine™

Question 2.1 Age-related exposure profiles are vital components of a risk assessment. The periods of high exposure and the contributors to that exposure are necessary elements of a risk assessment model. Does the panel agree that the demonstration case is a reasonable scenario and that children's exposures can be higher than adults' due to higher dietary intake on a weight basis and higher frequency of hand to mouth exposure events?

The Panel found this and the following questions very difficult to respond to. The questions hint at a request for professional judgment on the plausibility of a result that is based on a model simulation with little empirical basis for evaluation or testing. The Panel requested that its responses be interpreted in this light, and not be construed as a scientific endorsement of the findings or relationships implied by the case study simulation.

The Panel focused its response to this question on Demo Figure 2, which certainly looks reasonable: the level of exposure drops after infants learn to walk and keep their hands out of their mouths, then drops again after they enter their teens and spend less time in the house. The drop in exposure for teenagers suggests, however, that it is insufficient to consider residential exposure on its own and that institutional exposure may be just as important. In fact, when all sources of exposure are considered, it may well be that cumulative exposure is more constant over age (after infancy) than LifeLine™ indicates.

The LifeLine™ case study therefore produces a plausible result that in turn can focus attention on scientific testing of the hypotheses that are generated in the interpretation of the observed results.

Question 2.2 Understanding the source and route of exposure are key elements to aggregate and cumulative exposure assessments. Does the case study demonstrate that when sources of pesticides are independent, aggregate

exposure can tend to be dominated by a single route of exposure at given periods of time?

Here, as in the response to Question 2.1, the Panel members found this to be a reasonable conclusion based on the case study results. The comment was made that the graphs plotting "Aggregate Daily Dose" against "Fraction of Modeled Population" (Slides 49, 50 of the presentation, for example) are difficult to readily understand.

Question 2.3 Does the panel agree that this paper demonstrates that probabilistic models using existing data can characterize both cumulative and aggregate exposure to pesticides? And that the LifeLine™ model can be used to identify the critical sources of exposure and the influence of factors such as age and season?

The panel agrees that the paper demonstrates the ability to use existing data to model aggregate and cumulative exposures to pesticides. LifeLine™ can be used to identify critical sources of exposure and patterns over age and seasonal periods but this strength should not be construed to mean that LifeLine™ provides a scientifically valid profile of *all* sources and processes that contribute to seasonal and age specific patterns in aggregate and cumulative exposures.

While the presentation provides an interesting overview of LifeLine™'s capabilities, the panel would require a much more detailed look at LifeLine™ before it could attest to its validity. The Panel was firm in its opinion that, in the future, it would be best served by the ability to closely examine and test a working version of the LifeLine software and to have the opportunity to review an analysis of the uncertainty that is inherent in LifeLine™'s model-based estimates of aggregate and cumulative exposure.