SAP Report No. 2001-07

REPORT

FIFRA Scientific Advisory Panel Meeting
March 28, 2001
Held at the Sheraton Crystal City Hotel, Arlington, Virginia

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

HRI Lifeline™ - System Operation Review

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Olga Odiott, M.S.
Designated Federal Official
FIFRA Scientific Advisory Panel
Date:

Mary Anna Thrall, D.V.M.
FIFRA SAP Session Chair
FIFRA Scientific Advisory Panel
Date:

NOTICE

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

Federal Insecticide, Fungicide, and Rodenticide Act
Scientific Advisory Panel Meeting
March 28, 2001

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PUBLIC COMMENTERS

No oral statements were made during the meeting.

No written statements were received.

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 an assessment of scientific information concerning the Hampshire Research Institute (HRI) LifeLine™ - System Operation Review. Advance notice of the meeting was published in the *Federal Register* on March 5, 2001. The review was conducted in an open Panel meeting held in Arlington, Virginia, on March 28, 2001. The meeting was chaired by Mary Anna Thrall, D.V.M. Ms. Olga Odiott served as the Designated Federal Official.

The Panel reviewed key features of the LifeLine™ Model to include the software code, data requirements, data inputs, and output reports. LifeLine™ is a model for assessing aggregate and cumulative exposures and risks from pesticides. The Agency's presentation focused on the operating system and solicited panel comments and advice with respect to the transparency and operation of the model. Each Panel member was provided a copy of the LifeLine™ software and supporting documentation. The Panel was also provided with hypothetical, yet representative, residue and toxicological data sets for assessing aggregate and cumulative exposure and risk via the dietary, residential, and drinking water pathways.

CHARGE

The specific issues addressed by the Panel are keyed to the LifeLine™ software Version 1.0 and supporting documentation and are presented as follows.

Model Operation

Question 1: The LifeLine™ - CD includes model documentation in the form of a Users' Manual, Technical Manual, and Demonstration Case. Is this documentation sufficient to understand and operate the model?

Question 2: The LifeLine™ - CD includes "pre-packaged" data files for use in conjunction with the Demonstration Case as well as Knowledge base files which are used by the model to estimate potential exposure and risk. Were panel members able to generate a risk assessment report and identify routes of exposure and populations at risk, using the "pre-packaged" data files provided on the CD? Were panel members able to identify exposure contributors, and the data/assumptions used in the exposure/risk calculation by examination of output reports, output files (e.g. Exposure.bdf, Lives.dbf, Ractiv.dbf)and knowledge base files (e.g. Rtrecipe.dbf, Rtfoodit.dbf, Rtcgrac.dbf)? Please note these files are located in C:/HRI/RTL.

Question 3: LifeLine™ reports are based on seasonal maximums and means of exposure.

From the standpoint of producing a comprehensive risk assessment, what are the strengths and weaknesses of the reports generated by LifeLine™? Which reports are particularly useful for risk assessment and are there other types of reports that the Panel would suggest?

Question 4: LifeLine™ contains more than 90,000 lines of C++ computer code. The panel was provided annotated code for the risk assessment algorithms used in LifeLine™ . Do the algorithms in the annotated code perform the functions defined in the LifeLine™ Technical Manual?

Question 5: LifeLine™ relies heavily on survey data and EPA SOPs to estimate exposure and the frequency of exposure. These include Residential patterns (Current Population Statistics, US Census), The Third National Health and Nutrition Examination Survey ((NHANES III), also maintained by NCHS), American Housing Survey (US Census and Department of Housing and Urban Development), Nation Home and Garden Pesticide Use Survey (US EPA, 1992b), National Human Activity Pattern Survey (US EPA, 1994), the Continuing Survey of Food Intake by Individuals (CSFII), US Department of Agriculture (USDA), Residential Exposure SOPs (US EPA, 1998), and Exposure Factors Handbook (US EPA, 1997). Would the Panel please comment on the appropriateness of using these surveys/SOPs in the LifeLine™ model to estimate exposure and frequency of exposure to pesticides?

Question 6: LifeLine™ uses the USDA CSFII survey (a 24 hour dietary recall for 2 or 3 days) to estimate daily dietary exposure over an individual's hypothetical lifetime (ca. 85 years). This is done by matching criteria (age, gender, etc...) from CSFII with the individual being modeled by LifeLine™. Would the Panel please comment on this feature of the model?

Question 7: LifeLine™ estimates route specific risk via a route specific toxicological endpoint, but estimates the systemic or aggregate risk by route to route extrapolation using absorption factors. Would the Panel please comment on the appropriateness of this approach to estimating aggregate risk in this model?

RESPONSE TO THE CHARGE

General Comments

The developers are to be congratulated for their efforts with the LifeLine™ software. Modeling microexposure events is needed to estimate cumulative and aggregate exposures accurately, and the tool they have created should be very useful for these comprehensive exposure assessments. It is certainly true that this approach is data-intensive but the existence of such tools will encourage the collection and development of relevant data. The implementation of LifeLine™ includes two features that merit special commendation. Both of these features should be enhanced and extended in any future versions of the LifeLine™ software. The first feature is the ability to trace back the individuals who occupy the tails of the exposure distribution. Being able to discern the scenario that results in an especially large exposure is critical to producing realistic and useful assessments. The ability to trace back exposures should be further automated and extended to make scenario tracing a routine and convenient part of using LifeLine™. The second important feature is the auditing file, which permits the analyst to keep a full record of the settings and inputs that were used in a simulation. The Panel suggests that the auditing file could be generalized to incorporate user comments and simulation notes.

The Panel has three general concerns about the implementation that are not covered by specific questions in its Charge. The first concern involves the omission of provisions for modeling certain kinds of serial correlations. Longitudinal modeling requires a serious treatment of temporal autocorrelation. Despite LifeLine™'s substantial advances in handling the structural dependencies inherent in individual-based modeling of exposures, the software has incomplete provisions for handling temporal dependencies. The developers suggest that an analyst can bound exposures by conducting two simulations, one using perfect (maximal) correlation through time and one using independence. However, this approach does not generally produce bounds because of the possibility of nonlinear dependencies. Because the differences that can arise from different temporal patterns can be an order of magnitude or more, the issue may be very important. Further research may be required to develop analytical and simulation strategies needed to model temporal autocorrelation.

The second concern of the Panel is that the conservativism of the assessments produced using LifeLine™ has not been adequately documented. Some assessment should be made of the level of conservatism that the model realizes through various hard-coded assumptions. Even though many of the inputs are user-defined, there are still many model parameters defined in the software code that have been set by the developers. The extent to which a cumulative effect of conservative assumptions exists should be discussed (perhaps in an appendix) for various types of data input that can be used in the software.

The third concern is whether appropriate and sufficient checks have been integrated into the software to guard against errant user inputs (such as an absorption factor larger than one). Comprehensive checking of user input would obviously be very difficult, but almost any checks that the developers could incorporate into the software would be helpful in ensuring that LifeLine™ produces accurate and meaningful results. Conditional checking that goes beyond simple range checking of single inputs would be especially useful because such checking is usually very difficult to conduct manually.

One Panel member noted that EPA is not accounting for exposures from ingestion of organic produce. He noted that production of organic food has increased dramatically in recent years. The consumption of organic foods is presumably more seasonal and local than conventional foods, perhaps composing a much higher percentage of some individual diets than others. Overall cancer rates have dropped 15% during the era of synthetic pesticide use. Stomach cancer rates have dropped 50 to 60%, which may be due to the abundance of relatively cheap fruit and vegetables. However, about 40 to 60% of natural and synthetic chemicals are known or suspected rodent carcinogens, and around 20 to 40 different chemicals are used to maintain the safety of organic food. Some of these pesticides are known carcinogens or toxins. This Panel member noted that it would be prudent for EPA to consider exposures from organic produce consumption.

Model Operation

Question 1: The LifeLine™ - CD includes model documentation in the form of a Users' Manual, Technical Manual, and Demonstration Case. Is this documentation sufficient to understand and operate the model?

The goal of the LifeLine™ modeling effort was to develop a transparent modeling system for pesticide risk assessment that would be readily accessible to public and private risk assessors but robust enough to address aggregate and, in some instances, cumulative analyses under the FQPA. The Panel was given four documents to review: 1) a Users' Manual, 2) a Technical Manual, 3) a Demonstration Case Study, and 4) a portion of the Program Code. The following is a summary of the Panel's comments regarding these documents.

Software should either be very intuitive and forgiving of naive or intermediate users who are not experienced with these sorts of programs, or it should have clear and well ordered documentation. LifeLine™ is not very intuitive, even for experienced users, and it is very challenging for naive users. The user interface is not intuitive enough that a naive user could start without consulting the manual. This may be a good thing; the program is database-driven and it would be inappropriate for anyone to use it without knowing what they are doing and understanding the inputs they have chosen. Therefore, clear documentation is essential.

The cautions, notes, and tips in the Users' Manual are generally helpful for naive users. But even advanced users will need to consult the manuals, particularly the demonstration case, before conducting a full-scale risk assessment. The demonstration case manual was well planned and is suitable for leading an advanced risk assessor through the entire process. The Panel suggests incorporation of the demonstration case into the users' manual as an integrated document.

The illustrations of program screens in Chapter V of the demonstration case manual were valuable in helping a reader understand how to set up and run the LifeLine™ model. Perhaps the manual should be reorganized so these helpful screen illustrations come at the beginning of the manual. This way, a naive user would see them first and try running the model with some

example data files before attempting to customize the data files.

In the Panel's view, the documentation is generally adequate, but still needs rigorous editorial review to improve structure, style, and ancillary information (appendices with definition of terms and acronyms, more details on program structure, glossary of buttons, units for data input). Using the SAP process may not be the best way to beta-test the software as this effort requires a substantial time commitment and much focused effort. It would be worth investing the resources to have the program and the documentation reviewed professionally.

One Panel member undertook a "force failure" analysis using several subjects: an entomology graduate student very familiar with risk assessment and data bases, a senior undergraduate environmental science major interested in risk assessment, and a sophomore science honor student with no risk assessment background, but excellent computer skills. The software was presented to each of the subjects along with the three manuals. They were charged to evaluate the software and manuals on the basis of 1) user friendliness, 2) completeness, 3) explanatory power, and 4) ability to conduct a crude risk assessment for an organophosphate insecticide with data provided in an Excel spread sheet prepared by the panel member. These students invested an estimated 48 hours of time in this process. Their comments have been provided to the developers.

Another Panel member gave the software and manuals to a statistics graduate student with an interest in risk analysis. Instead of running examples, he produced a 3½-page executive summary of the Users' Manual. This proved to be very useful and saves having to go through many pages of the Users' Manual to discover the many capabilities and limitations of LifeLine™. The Panel suggest that the Users' Manual begin with a summary chapter, based on the document *Overview of the Fundamentals of Version 1.0 of LifeLine™* provided by HRI. The Panel have provided the student's summary to the developers along with the edited manuals.

The following is a summary of what the Panel considers to be advantages of the LifeLine™ Software:

- Flexible data entry and management.
- Compatibility with an array of other data basing platforms.
- Ability to easily conduct "what if" scenario analysis by constructing parallel data analysis (runs) and comparing output in another program (SAS, SYSTAT, JMP, etc.).
- Sharing risk assessment files easily between users.
- Transparent risk analysis except in the case where proprietary data were used in a portion of the study.
- Flexibility within the program to default to a general case or single numeric entry as opposed to a distribution when the later is not available.
- Logical general structure with the Food Residue Translator, Activity Descriptions, Tap water Concentrations and AI and Product Description input modules into the LifeLine™ model with an array of output options.
- Non-experts can fairly rapidly put together a crude risk assessment.

The following is a summary of what the Panel considers to be general drawbacks of the

Software:

- Extensive data entry requirements.
- Requires advanced data handling capabilities.
- Manuals did not have a sufficiently consistent format to aid the user in transitioning from one manual to another.
- Acronyms and technical terms were not well defined from manual to manual nor were they uniformly addressed; the manuals need a glossary of terms common to each and careful bridging between manuals.
- There was no consistent "session window," log mechanism, or software architecture running in the background to recapitulate a session other than saving input and output files.
- The user interface is quite good but can still be improved. For example, the "Start Analysis" button should be called "Generate New Lives"; since if you push it after generating lives, thinking it will start analyzing them, you will lose them. While the flexibility in the graphing option is excellent, you can get inappropriate graphs, e.g., a line graph connecting all individuals in serial order, and it isn't obvious what your options are to improve the presentation of a graph.

Users' Manual:

The wording of the manual was at times convoluted and challenging to understand due to an array of grammatical and typographical errors, especially for naive risk assessors. The layout of the manual was often counterintuitive. For example, it repeated instructions on how to save and print at the end of each section, but it rarely discussed how to import from and export to Excel. The output formatting should be more condensed. For example, the printout from one analysis derived from the demonstration case required 10 pages, while the exported version to Excel required only 4 pages. Various buttons and icons in the program seem to have no logical interpretation or require a "reach" to intuitively connect them to their functions (e.g. an appropriate and standard logical connection being a floppy disk and the "save" function while a stick figure touching its toes represents "edit activity descriptions" was not apparent until a search of the manual revealed the connection). In addition, there were many acronyms used in the manuals that even a fairly advanced user would need to refresh his or her mind to maintain clarity of process. Footnotes were frequently found on the wrong pages, and occasionally a graph or table referred to in the text was not included in the manual. Also, there were editorial comments, set off with "<<" embedded in the various manuals.

To an advanced user, some functions were superfluous, e.g., the steps involved in the concentration determination of active ingredient(s) used per application (page 33 of the users' manual). This required one to fill in blanks with information about how much active ingredient was contained in the product and how much of the product was applied per "dose." Then, the "wizard" calculated concentration per application. The expert found it much easier to calculate the number directly. On the other hand, a less experienced user appreciated the function and the opportunity to document the process for record keeping purposes. The Panel was divided on this issue, and it defers to the developers on this issue.

The help feature was unavailable for the Risk-Dose-Exposure report.

File extensions:

For each module, there are different file extensions and a folder. The manual does not make this clear. For an intermediate computer user who has received someone else's data files this could be a key frustration feature. The intermediate user probably would not be savvy enough in opening the database and program. A uniform process for shipping and receiving data files should be developed. One suggestion is the inclusion of a preamble in the introduction indicating where different extensions are used and what their formats are. Another suggestion is to create a data dictionary for the input and output .dbf files. This innovation could be extremely helpful, both for understanding the operation of the programs and for creating additional reports on the results. The function and content of each file, as well as its data fields, should be explained.

A better explanation of the End Use Product Equivalency (EUPE) concept would be helpful in both the Technical Manual and the User's Guide. It should be made clear how the way a EUPE is defined affects the exposure assessment. The EUPE Application Method Wizard window for product application is confusing. More explanation of what is supposed to be entered would be helpful. For example, "rate of applied product" is not an immediately understandable term. Does it refer to packaged product or product as prepared for use, or does it matter?

The users were unanimous in suggesting that the manual needed a glossary of buttons utilized in this program or some kind of pictorial index to the buttons. Their individual functions could be addressed and mapped into an overall pictorial index with a user interface map.

There were many appropriate pictures or figures addressing how to use, manipulate, or access the program, yet there were no overarching diagrams such as those presented in various meetings held in the last year. It would be a distinct advantage to new risk assessors to have similar screenshots of the program itself and descriptions of how it is used.

In general, the Technical Manual and Demonstration Case were in very good shape considering the formatting problems with the Windows software. Presumably these problems will be addressed in a future release of the software. In summary, the Panel commend the developers for their efforts and particularly for the completeness of the manuals provided to the Panel. LifeLine™ will be a significant and appropriate addition to EPA's risk assessment software. Additionally, it will provide private, non-goverment organizations, and academic users the opportunity to participate directly in the pesticide risk assessment arena.

Specific suggestions concerning the User's Manual and the Technical Manual are presented in the "Additional Comments" section of this report.

Question 2: The LifeLine™ - CD includes "pre-packaged" data files for use in conjunction with the Demonstration Case as well as Knowledge base files which are used by the model to estimate potential exposure and risk. Were panel members able to

generate a risk assessment report and identify routes of exposure and populations at risk, using the "pre-packaged" data files provided on the CD? Were panel members able to identify exposure contributors, and the data/assumptions used in the exposure/risk calculation by examination of output reports, output files (e.g. Exposure.dbf, Lives.dbf, Ractiv.dbf)and knowledge base files (e.g. Rtrecipe.dbf, Rtfoodit.dbf, Rtcgrac.dbf)? Please note these files are located in C:/HRI/RTL.

One Panel member who had previous experience with the LifeLine™ program as a beta tester commented that the system is not very intuitive. It is essential to monitor where you are and what you've done as you proceed through the programs. While the program keeps track of the files that were used, it did not keep track of modifications made along the way. This had to be done manually so that the item changed was noted as to its initial value and what it was changed to. It is very important to have a log file in which all user specifications for the analysis are recorded.

Another Panel member was able to go through the example data set and generate a risk assessment report. Having example data sets is a very useful teaching tool, because it would be much more challenging to learn the software and understand the data requirements without it. The Panel member was pleased to see that the software allows for extensive user control of the data input.

In order to identify highly exposed subgroups and the contributing factors to high exposure, it would be very helpful to have a reporting module that would collect and display all the input and output values for selected individuals.

Another Panel member was able to identify exposure contributors and the data/assumptions used in the exposure/risk calculation by examining output reports, output files, and knowledge base files. The ability to compare age related doses and then being able to look at the differential influences of routes of exposure for the various age groups was particularly valuable. The ability to modify some of the household measures and see their effects was also valuable. One concern was the potential limitations on estimating lifetime exposure if, for instance, only one database is used for food habits (CSFII 1990 or 1996), or one period of measures for pesticide residues in foods, which are essentially static systems that may not reflect the changes that occur during a lifetime. Eating habits for a 10-year old in 1990 may be very different than eating habits of a 10-year old in 2000. One would want to know whether the changes in habits or residues are great enough that the use of multiple databases would be of value. That is, does the probabilistic approach using one database provide enough variability to cover changes in food habits and pesticide residues that may have occurred over the past 10 years. Otherwise it would be that one is only looking forward from someone born in 1990 or thereabouts.

The documentation needs to clarify the difference between projection and prediction. The objective of LifeLine™ is projection, to look at the long-term effects of given patterns of pesticide use and given patterns of human behavior. It is not intended to predict what will happen in a socially evolving population. However, from the point of view of an epidemiologist, prediction would be valuable.

The open architecture, transparency, and the ability to review input and output files are extremely useful, and provide a good basis for the software's use as a regulatory tool.

It would be helpful to have some discussion in the Technical Manual of the difference between the output of a "conventional" probabilistic exposure assessment and the output of LifeLine™.

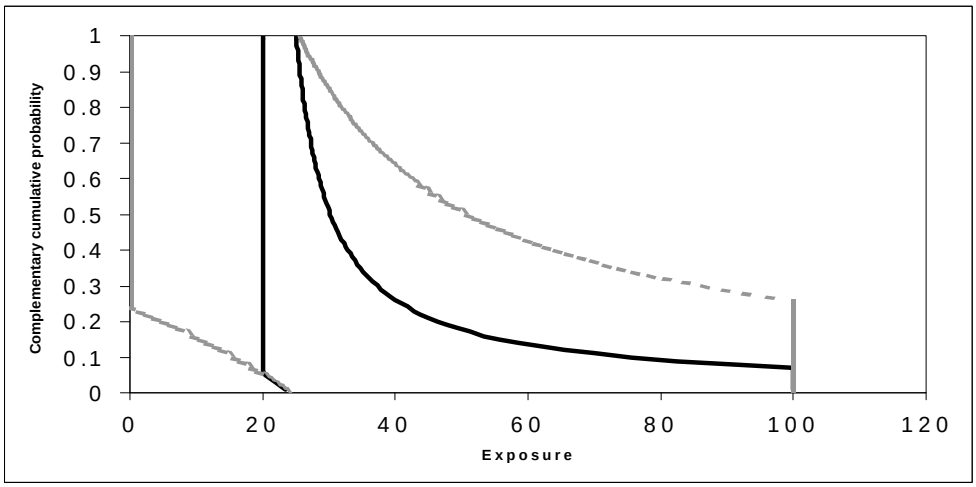
Question 3: LifeLine™ reports are based on seasonal maximums and means of exposure. From the standpoint of producing a comprehensive risk assessment, what are the strengths and weaknesses of the reports generated by LifeLine™? Which reports are particularly useful for risk assessment and are there other types of reports that the Panel would suggest?

LifeLine™ evaluates exposures of individuals on a daily basis from birth through death or age 85. Summary statistics for this lifetime profile are stored as summary statistics for the 90-day seasonal periods. Ideally, daily exposures for each simulated individual would be stored and available for independent summarization and analysis by the LifeLine™ user, but the storage requirements for a lifetime analysis of large samples of individuals makes this unrealistic. The choice of the mean and maximum reflects both a need to restrict the number of stored distributional statistics and enable sequential day by day development of the statistics required for their computation. They are certainly reasonable choices but do not provide the full flexibility that LifeLine™ users may want in their analyses. For example, the Panel felt that, in addition to the seasonal averages and maxima for each averaging period, it would be useful to have the annual averages and maxima. Particularly if there were little seasonal effect, the annual measures would be more concise summaries of exposure. Another option would be to capture every day for one selected averaging period. If 1000 individuals were simulated, this would produce a file with about 1000×365×75=27,375,000 daily records, each with the identifying variables plus the average total exposure for the averaging period ending on that day. Alternately, perhaps a way could be devised to keep only the top 5% of individuals, based on a user-selected measure. For example, the top 5% might be based on lifetime average exposure, or annual average exposure at age 6, or maximum daily exposure at any point in some age range, etc. Some effort should be made to enable users to generate reports of extreme quantiles of the distribution of exposures for single days or longer user-specified time periods (95^{th}, 97.5^{th}, 99^{th}, etc.). Because these tails of the exposure distribution are especially interesting to risk analysts, it might be reasonable to expend some computational effort and memory to obtain a better picture of the tails. For instance, although computing the median of the distribution would be cumbersome, it would be very simple to keep track of the five largest values, rather than only the maximum value. This would substantively improve the characterization that can be made for the distribution tails.

The Panel also felt it would be easy to compute the variance on the fly during a simulation. Knowing the variance would obviously be very useful in characterizing the otherwise censored distribution of exposure. In particular, it would permit the generation (via Chebyshev-like inequalities) of bounds on the extreme quantiles. It might also be especially useful to keep track of the geometric mean and geometric standard deviation, especially if the exposure distributions

are likely to be similar lognormal distributions or at least highly skewed. This might be problematic, however, if there are many zeros among the exposure values. The presence of many zero values could perhaps be used to trigger an option for computing geometric moments based only on nonzero values.

The developers mentioned that, previously, the minima, as well as the mean and maximum were saved as part of the LifeLine™ internal summary but have since been omitted because they are of limited interest to risk analysts. It should be pointed out, however, that the minimum can be very useful to risk analysts to bound the risks of exceedance. For example, the graph below depicts distribution-free bounds on the exceedance risk (i.e., the probability that an exposure is larger than a given amount). The abscissa is exposure level, and the ordinate is probability, cumulated from the right. The outside bounds (gray) enclose all distributions that have a maximum of 100 and a mean of 25. These bounds are what can be inferred from knowing only the mean and the maximum of a random variable, without making any assumption about the shape or family of the underlying distribution. They tell us how probable large exposures might be. The inside bounds (black) circumscribe all distributions that have a minimum of 20 units, a maximum of 100 units and a mean of 25 units. These bounds are what a risk analyst could infer from the LifeLine™ results if it outputs these three statistics. The interesting thing about this graph is that having knowledge about the minimum value allows us to substantially improve our estimate of the risks of large exposures. Of course, this improvement will be small if the observed minima are usually close to zero. (Knowing the variance would further tighten both the black and the gray bounds.) The reports generated by LifeLine™ apparently are limited to time series plots of exposure values. These are reasonable and effective outputs from the simulations, but other kinds of summaries might be even more useful to risk analysts. In particular, analysts would expect to see graphs of the empirical frequency distribution of exposures (means or maxima). These distributions are usually plotted as complementary cumulative distribution functions, as plots of exceedance risk for exposures.



One very useful feature of the LifeLine™ software allows analysts to click on a data point and be given information about the variable, age, season and value of that point. It would be very helpful if the software could extend this feature to trace back to how this point arose in the simulation (Could clicking on a data point be extended to see whether, for instance, the datum came from a baby that eats 20 pounds of bananas?).

A member of the Panel expressed an interest in an extension of LifeLine™ that would add the average and maximal values of the internal body burden of the chemical or effect, given some simple linear rate of elimination of the chemical or effect, expressed as a half-life. This might be more directly related to the potential for toxicity for (1) chemicals whose effects depend on internal concentration in some organ or (2) chemicals that cause effects by a mechanism such as cholinesterase inhibition that has a knowable rate of reversal of a change from baseline in a well defined parameter. It would also be feasible and desirable to have mean logs and standard deviations of the logs of nonzero values to allow projections of the risks of exceeding various values, given an assumption of lognormal distributions.

The Users' Guide mentioned that the software is capable of performing cumulative risk assessments (multiple AI's with similar toxicity characteristics), but this appears to be cumbersome in the current version. This feature could be better facilitated in the software. The logical extension of LifeLine™ to cumulative analysis will be possible in most instances. The unique, "individual based," residue-modeling approach will provide a means to analyze co-occurrence exposure assessment linked to distinct exposure scenarios and queries. Thus re-sampling individuals can build exposure profiles for different populations and can provide probabilities of exposure, dosages of exposure, and exposure histories for these populations. This architecture allows analysts to explore periodic, episodic, and constant exposure scenarios, moving risk assessment closer to real-time situations. The panel also noted that the Food Residue Translator could be adapted for residue mitigation profiles by allowing users to edit residue #1, #2, #3, etc. with a unique identifier. The analyst would then compare past residues files with residues from mitigated "what if" scenarios, thus providing insight into procedures that could mitigate residues in various field application scenarios.

Question 4: LifeLine™ contains more than 90,000 lines of C++ computer code. The panel was provided annotated code for the risk assessment algorithms used in LifeLine™ . Do the algorithms in the annotated code perform the functions defined in the LifeLine™ Technical Manual?

The frequency of typographical errors in program code is greatly reduced in a strongly type-checked language such as C++, especially if the coding is conducted in an integrated development environment, in which references to variables are managed automatically by the computer. Nevertheless, the misspellings in the LifeLine™ program code and its documentation, which are far more common that should be expected, are disquieting because they suggest that the program has not yet undergone a comprehensive battery of checks during its development. It would improve the appearance of the software if these could be removed, at least from the documentation and the string resources (prompts, labels, warning messages, etc.) that are seen by users.

Error trapping in the LifeLine™ code does not seem to be very well developed. As an example, consider the single-line trap

```
if (residue < 0 || intakegrass < 0 || gia < 0) return;
```

which appears in the CaiPostAppDose::CalculateOralgrass routine mentioned on page 56 of the annotated code. In other routines, variables such as body mass, skin surface area, and time spent in an activity are checked for positivity in similarly brief tests. If any of these tested variables are negative, the routine ends without changing the exposure. It seems, however, that any negative value would be symptomatic of a serious problem requiring a more substantial response. Presumably there would also be an error condition if the variable *gia* (an absorption fraction) were greater than one, but this condition is not trapped. The software annotation does not indicate whether negative values or other out-of-range conditions are trapped elsewhere in the code, or whether they are not trapped at all and would go unnoticed if they occurred.

A cursory review of the unit conformance in the annotated code did not reveal any obvious inconsistencies. However, because even a single error can significantly degrade the accuracy of the results, the developers should undertake a comprehensive review of the code for dimensional concordance and unit agreement. Many of the variables used in the code are described as unitless. This is unfortunate because unitless parameters are easy to misunderstand (Hart 1995). It would be preferable to describe them as ratios of like dimensions, especially in the user interface. For instance, if a parameter is expressed as the ratio of grams of chemical per grams body mass, it would increase the intelligibility of the program if the interface indicated this fact. Allometric relationships, which usually employ complicated unit conversions, are used in several places in the LifeLine™ code. These relationships require manual checking to ensure that the appropriate unit conversions have been made.

The answer to the question of whether the specified algorithms perform the functions described in the technical manual is that they *seem* to do so. However, the reviews that Panel members have been able to mount in a short period of time certainly do not constitute a thorough review.

Validating all of the printed code excerpts would require more expertise and concentrated effort than can be expected of the Panel. Consequently, there can be no imprimatur by the Panel on the correctness of the LifeLine™ software.

The developers and EPA program managers should consult experts in software reliability about the quality assurance procedures in place for the development of LifeLine™. Standards and procedures to ensure software reliability are evolving (Hoffman and Weiss 2001). We understand that each module was checked "by hand" as it was developed, and that overall testing is being done through uncontrolled beta testing by a wide range of users. Beta testers will probably concentrate on the model, the inputs, and the user interface, and are not likely to uncover small errors due to incorrect coefficients or incorrectly specified units or typographical errors in formulas or memory management errors that lead to results that look plausible but are incorrect without being impossible or crashing the program. Some members of the Panel suggested that paid reviewers with appropriate expertise in computer programming and software reliability be contracted to undertake a professional review of the LifeLine™ software.

Despite the Panel's inability to conduct a full validation of the annotated program code, it is very important that the developers have provided it. Having an open architecture is essential to scientific progress in the assessment process. The Panel encourages the developer to consider the annotated code as part of the documentation of the LifeLine™ software. The developers have suggested that wide-scale use by motivated analysts will provide the most thorough testing of the software. This will only be the case, of course, if these users have free access to the internal design and actual code of the program. The Panel applauds the developers for providing registered users access to the entire code upon request.

Model Architecture

Question 5: LifeLine™ relies heavily on survey data and EPA SOPs to estimate exposure and the frequency of exposure. These include Residential patterns (Current Population Statistics, US Census), The Third National Health and Nutrition Examination Survey ((NHANES III), also maintained by NCHS), American Housing Survey (US Census and Department of Housing and Urban Development), Nation Home and Garden Pesticide Use Survey (US EPA, 1992b), National Human Activity Pattern Survey (US EPA, 1994), the Continuing Survey of Food Intake by Individuals (CSFII), US Department of Agriculture (USDA), Residential Exposure SOPs (US EPA, 1998), and Exposure Factors Handbook (US EPA, 1997). Would the Panel please comment on the appropriateness of using these surveys/SOPs in the LifeLine™ model to estimate exposure and frequency of exposure to pesticides?

The Panel would like to commend the LifeLine™ group for their thorough integration of existing

population data resources. It is the general consensus of the Panel that LifeLine™'s choice of national surveys for key population data inputs represents the best choice among the available data sources. LifeLine™'s developers have recognized many of the shortcomings associated with the use of these data and have conducted important analyses to support decisions such as "binning" for simulation draws and modeling of physical relationships. The documentation would be improved, however, with a series of comparisons between distributions (such as height for children of various ages and weight as a function of height) as generated by the LifeLine™ model and distributions of the same parameters in particular populations observed in the original data or other data published subsequently. The authors should also describe whether and how they used the population/sampling weights incorporated in some of the data bases (e.g., NHANES III).

Birth records (natalities) from National Center for Health Statistics (NCHS) vital statistics for 1996 are used to generate a sample from a "nationally representative" population of individuals. The birth and death data contained in these vital statistics series are affected by problems of misclassification for persons of Hispanic ethnicity and individuals of races other than Caucasian or African American. The problem of misclassification is noted in the LifeLine™ Technical Manual.

Each LifeLine™ user will be concerned with the age, cohort, and time frame reference for the population of interest. The LifeLine™ User's Manual should devote more time to the age, time, cohort relationships and how the analysts should interpret their results in light of the way the model confounds these elements. The structure of the current LifeLine™ model is really focused on age. The model assumes that time-dependent changes are a function of aging and not of secular change in food consumption, activity patterns, etc., for persons of the same age. The model does not distinguish cohort effects. The methodology of generating a population sample from birth records creates a stationary population based on 1996 birth rates by mothers race and ethnicity, location, and the approximate SES status of the mother (inferred from education). Therefore, analysis of cumulative exposures for a population of 45- to 54-year olds models lifetime exposures beginning at birth in 1996. However, due to the relative time-independence of sequential daily, seasonal or annual exposures analysts can restrict their analysis to defined time periods of the simulated lives to study cumulative exposures for older age groups.

A cohort analysis (45- to 54-year olds) using LifeLine™ assumes:

1) Population distribution has remained stationary in composition over the past {k} years, where {k} is the age range of the birth year cohort of interest. This is not reasonable if we want to study a historical birth cohort (45- to 54-year olds born 1946-1954). It would be reasonable if we are interested in looking at effects {k} years after introduction. A question that could be answered is *How does the lifecourse distribution, based on the natality record sampling, replicate current cross-sectional demographic distributions for the U.S. populations?* This could be checked by comparison to estimated distributions from the March U.S. Current Population Survey (CPS) Demographic Supplement.

2) Diet data, pesticide use data, housing characteristics, activity data for the age group are

current (reasonable) if we assume minimal secular change;

3) Residue data inputs are good for current representation if we assume minimal secular change.

LifeLine™ also introduces age specific mortality to the simulated population of individuals and their annual sequences of exposure observations. The age, gender, and race-specific mortality rates used by LifeLine™ are also drawn from the NCHS Vital Statistics data series. As the LifeLine™ Technical Manual points out, mortality rates for some ethnic and racial groups are biased due to misclassification of individuals on the death records data.

The Current Population Survey (CPS) or U.S. Census is a good choice as the source of data for modeling the residential mobility patterns of the U.S. population. Pooling multiple years of CPS data would enrich data for small bins. Given the broad set of demographic and geographic characteristics used to define bins, inclusion of CPS weights in making the draws may not be essential for acceptable population representation; however, this assumption should be tested thoroughly since mobility (loss to follow-up) is probably a contributing factor to variability in the final CPS analysis weights.

The LifeLine™ model uses a model based on the NHANES III to assign each physical characteristics to each simulated individual. The NHANES studies provide the best nationally representative data set for detailed physical measurements on individuals. NHANES studies do include differential sampling that may be unrelated to the demographic and geographic characteristics used to define sampling bins. Therefore, the impact of the NHANES III survey weights on the simulated distribution of heights and subsequent modeling of weights should be evaluated.

CSFII appears to provide best available, national representation of daily food consumption. Version 1.0 uses CSFII data that are over ten years old. More current dietary representation will be brought into play when the 1994-1996 CSFII and child Supplement data are used. The Panel is not aware of national data on dietary intake that would provide longer sequences (than the three days used in CSFII) that would provide empirical control on day-to-day change in diets or longer-term food consumption patterns. LifeLine™ might consider using the three-day sequences that CSFII provides for annual data collections (missing data for multiple day sequences may be a problem).

For national representation, the Annual Housing Survey (AHS), National Human Activity Pattern (NHAP), and the National Home and Garden Pesticide Use Survey (NHGPS) provide the best, current national population representation of housing stock, activity patterns, and household pesticide use at the level of detail that is required. LifeLine™'s authors have taken the important step of putting in time dependent restrictions on sequences of potentially large exposure events (e.g., reapplication time delay for pesticide application and the degradation of the active ingredient).

The Panel noted that LifeLine™ data inputs and default assumptions from the EPA SOPs and

EPA Handbook are often based on limited data. There are many data gaps including no data on hand-to-mouth activities of older children and adults, limited data on tap water concentrations and no data on important occupational exposures. The LifeLine™ model requires information on tap water concentrations. At this time, such data are generally not available. The Panel encourages the EPA to develop a reliable data source for pesticide concentrations in tap water. Given the current limitations, the Panel agreed with the general approach with which the software uses water quality data for assessing exposure from tap water.

The LifeLine™ group made a good decision to separate data sources on pest pressure and pesticide use. As they note, pest pressure will be relatively stable from year to year within a given region and season, while the use of pesticide products will vary depending upon product availability, marketing, and even public sentiment about pesticides. Separating the data sources allows them to be updated independently, and also allows constructing hypothetical scenarios for the use of pesticide products. In using the NHGPUS as the data source for pest pressure, assumptions had to be made about the seasonality of the pests, because the survey did not record the dates of treatments. There is a need for data on seasonal and regional occurrences of pests. Another serious data gap is for residential pesticide use. Consumer surveys like that being conducted by the REJV should provide useful information to help fill this gap. To be useful for the LifeLine™ model, surveys of residential use will need to collect sufficient data on the target pest of each application to allow the product use to be linked to an independent pest-pressure database.

The Panel expressed concern that NHAP generated too many unrealistic scenarios: People were seldom out of the house for travel, work, school or vacation; a low-income 13-year-old spent 2 hours reading a newspaper; and an 80-year-old woman in the Northeast ate outdoors at night in the winter, to mention a few. It is clear that behavior like this does happen, but if LifeLine™ generates one activity pattern per season then the person is assumed to do this every day for the season and it will require simulation of many individuals to balance this out with more common behavior. What are the limitations and biases in NHAP? One Panel member suggested that the survey data should be edited to remove the more extreme behaviors, even though there is the risk of introducing bias if that is done. It is not clear whether it is a limitation in the data or in the construction of LifeLine™, but it would be better if the first 2 or 3 years of life could be subdivided into finer time increments. This would avoid scenarios in which an infant is eating pizza in one season of the year and baby food in the next.

Question 6: LifeLine™ uses the USDA CSFII survey (a 24 hour dietary recall for 2 or 3 days) to estimate daily dietary exposure over an individual's hypothetical lifetime (ca. 85 years). This is done by matching criteria (age, gender, etc...) from CSFII with the individual being modeled by LifeLine™. Would the Panel please comment on this feature of the model?

The developers are to be commended for taking an empirical approach to grouping ("binning") CSFII records into categories observed to differ on food consumption. Their method of reducing complex daily dietary records into a few summary measures such as number of different foods

and total mass of food consumed per day is also commendable. It is not clear, however, that the number of eating occasions per day nor the number of foods per eating occasion should be used as outcome measures in this exercise, since they are not used in the exposure estimate in any way. A clearer and more useful grouping might emerge if these outcome measures were omitted. In addition, it might be valuable to research the relationship of food consumption and other variables in datasets containing more variables than the CFSII. This could help reveal how likely it is that selecting CSFII records based on the chosen characteristics will simulate a realistic individual.

There are several other issues of concern. In general, dietary recall is rarely accurate, but perhaps all that matters for LifeLine™ is that what people in the survey recall is representative of their true eating habits. One Panel member suggested that when the model is drawing only one dietary pattern for an entire season it might be best to eliminate the more unusual patterns from the draw. Using the matching criteria is a good idea but, as a general rule, the model should be kept more general and less specific. This will keep the bins larger and give more dietary scenarios to draw from each time. It is also important that serial correlation be allowed in the model. CSFII data are a recall of at most 2 or 3 days and are inadequate for modeling serial correlation. Finally, some corrections could be added to the model for the systematic bias of reporting of dietary consumption with body weight, with the heavier people tending to report less consumption of food than is actually the case.

Question 7: LifeLine™ estimates route specific risk via a route specific toxicological endpoint, but estimates the systemic or aggregate risk by route to route extrapolation using absorption factors. Would the Panel please comment on the appropriateness of this approach to estimating aggregate risk in this model?

The Panel believes that LifeLine™ has made good use of the current available information. What is unclear is whether at some time in the future users will be able to take into account target organ doses based on the various routes of exposure—effectively interfacing with physiologically-based pharmacokinetic models.

A more modest incremental step toward this should be considered. In aggregating systemic exposures from oral dosing with systemic exposures arising from inhalation or dermal exposure, there is an opportunity to make one further adjustment. When material is absorbed from the gastrointestinal tract, the blood carrying the pesticide must pass through the liver first before it goes to the rest of the body. By contrast, only about a quarter of the blood carrying the pesticide absorbed via other routes goes directly through the liver, at least on the first pass through the body. This could make the most difference for a highly extracted chemical, i.e., one that is removed appreciably on its first pass through the liver following oral exposure. For such a chemical, absorption via the oral route could be less than half as effective in delivering material to the body than absorption via other routes, even if raw absorption fractions for different routes were taken into account. (On the other hand, in a case where a pesticide is activated in the liver to a more toxic metabolite, the effective systemic dose should be adjusted upward rather than downward for oral absorption.) The reader should be made aware of this issue in the next version of the documentation, probably with instructions that a different absorption factor might

be appropriate for the oral route depending on whether the systemic effect being assessed occurs in the liver versus some other organ (for the liver, no first pass adjustment should be made, but for another organ, oral route exposure should be represented with this additional factor considered). In future versions of the software, dialogs can be added to help the reader think of this possibility and put in the appropriate adjustment factor for the oral route to reflect first-pass metabolism.

Additional Comments Concerning the User's Manual and the Technical Manual

Specific suggestions concerning the Users' Manual

1) pg. 3: The System Hardware Requirements section does not indicate with what operating system this program suite is compatible.

2) Throughout the book, bulleted information is structured both as a section of bullets and as a long sentence. One style or the other should be chosen.

3) pg. 16, **Program Issue:** If one wishes not to evaluate indirect dermal exposure to the compound, can one turn off this feature? The manual stated that this function can be turned off, but this feature was not apparent to our users.

4) pg. 17, **Program Issue:** The absorption fractions could be presented as a percent in addition to a fraction.

5) pg. 18-19: Discussion of the minimum and maximum exposure period was confusing to some users. A more general description of this process is needed.

6) pg. 20+, **Program Issue:** Why are the boxes that contain spreadsheet pieces not the same size as the spreadsheets they contain?

7) pg. 20: There was no mention of how many pages the non-cancer toxicity data involved in this wizard.

8) Throughout the program: notes and titles identifying the beginning of new topics and subjects should be uniform and boldly defined.

9) pg. 29: Wizard suggestion: There could be a better indication that certain parts of the wizard are inactivated by various choices in the course of an analysis. This was often not intuitive or even logical to all of the users. In summary, we were confused for quite some time as to why this option (commercial application data) did not appear every time.

10) pg. 32: Why does the "post-Application residue" page not show up each time this routine is used?

11) pg. 33 **Program Issue:** Why is the minimum time for reapplication unavailable if you choose "commercial application"? Aren't there situations where reapplication would occur for commercial application too?

12) pg. 34: See comment #3 and apply to the decline rates listed on this page.

13) pg. 35, **Program Issue:** The printout of Active Ingredient and Product Description should list each End Use Product Equivalent in a larger font, left-justified (not centered) where it will be distinctive and easily located.

14) pg. 36: No information is given on how to export to Excel or dBase IV, when much information was given on saving and opening files. This seems an important oversight and easily addressed since the demonstration case does have a table addressing this concern.

15) The save feature should default to a name, such as the name of the active ingredient that was currently under analysis.

16) pg. 41+, **Program Issue:** the icons used in this section seem very disconnected from their function…perhaps a more intuitive choice and glossary of icons similar to the demonstration case would be appropriate.

17) pg. 45, **Program Issue:** "Child Care" is listed twice on the activity pattern list.

18) pg. 54, **Program Issue**: Why is there a popup window that opens each time the Food Residue Translator program opens? Why is this information not simply in the user's manual?

19) pg. 56: Why does the spreadsheet fail to fill the monitor window until after "View Commodities" was pressed?

20) pg. 59: How does one edit and assign a unique name to "Residue #1", Residue #2, etc.?

21) pg. 62: "File/Import Residue Factors" on the menu bar was unavailable throughout our trials of the program. Have we missed some application?

22) pg. 62: Keep the table together and move text appropriately.

23) pg. 62: How does one import data to this program? All of our test case users had difficulty with this option.

24) pg. 62-63: Footnote #10 is important information that should be incorporated into the text of the manual and not relegated to a footnote. We suggest that it could be incorporated at the bullet level in your organization format.

25) pg. 66: The developers may wish to consolidate and simplify the text after Pfactor1.

26) pg. 70: Under "Summary Reports of Results, " it is mentioned that one has already specified the notation "dist" if a distribution was specified. When was this performed, and what residue value does it refer to?

27) pg. 71: The word "Caution" should be with the rest of the box on page 72

28) pg 72: Regarding the box on this page, it seems that this is just a reiteration of the

previous paragraph.

29) pg. 72, **Program Issue:** The print dialogue box brings up a "Print" dialogue box. If this box is going to be brought up from the "Print *Preview*" option, then the box itself should be labeled as such. Also, why are changes made in the "Print Setup" box not translated into the "print preview" box?

30) **Program Issue**: When exiting without saving, we got a warning that we had made changes since the last save, but once the dialogue box was cleared, the program closed without giving the option to perform the tasks that it suggested in order to prevent a loss of data.

31) pg. 73-103: Except for a few minor typographical errors, this section of the manual was well written. It was very clear, concise and thorough, indicating not only what method should be used, but why, and what might happen if it weren't done. Also, the descriptions of where to enter data were clear and easy to follow. All in all, our favorite section of the manual.

32) pg. 83, **Program Issue:** The scroll bar on the Print Preview window is inconsistent. It scrolls from the top to the bottom of a single page and then scrolls from the top to the bottom again for the next page. However, when scrolling up, it skips directly to the top of page 1 without scrolling.

33) pg. 105-109: Combining multiple active ingredients into one general category does not seem to be a reasonable substitution for entering multiple active ingredients. Also, this section is very poorly worded, and difficult to understand for naïve users.

34) pg. 106: Is this a misspelling of RPF, RFP?

35) pg. 110-140: This section is very well-written. Refer to #31 above.

36) pg. 115: Table 5 does not concur with program options for "Cancer" and "Average vs. Max"

37) pg. 120: "Generating a Table or Graph" section should precede the section on "Basic Views" as no graph or table can be used until the "Create an exposure analysis view with current options" button is pressed.

38) pg. 128: The "Sort on total" button (the one with 1,2,3 on it) needs more description for usage. Also, it does not specify that a graph or table must be selected before this button becomes activated. This is also true for the "Print" button and "Export" option. These issues are very confusing for first time users of the software.

39) pg. 132, **Program Issue**: We were unable to make the Background feature work with any bitmaps that were of any significant size. Is there a restriction on file size for

this function?

Specific suggestions for the Technical Manual:

1) pg. 5-3: Recipe files or translation files are a much appreciated and unique addition to the LifeLine™ model. This feature will assure greater transparency.

2) pg.5-4: Note editorial comments on first paragraph in the hand edited documentation.

3) pg. 5-5: Lost formatting and needs a greater explanation for probability factor and processing factors for naïve users.

- Subheadings throughout do not have the same format.
- It would be helpful to have web the LifeLine™ site and Codex reference for MRL data here.
- Dangling sentence at the bottom of the page?
- Greater discussion of EPA's SOP on "zero" residues should be included.

4) pg. 5-8: A demo of downloading FACTORS.DBF into the "other" column would be helpful

5) pg. 5-9: An icon from the tool bar for saucepan would be useful here (2nd paragraph).

- Naive users were confused about why the program would not default a zero to ½ LOD or LOQ?
- Is there a feature to effectively turn off a residue for a what-if scenario? How? Please illustrate.

6) pg 5-10: The reference to the Users' Manual in the second paragraph should have a page citation.

7) There is no TABLE 4-8.

References

Hart, G.W. 1995. *Multidimensional Analysis: Algebras and Systems for Science and Engineerin*g. New York: Springer-Verlag.

Hoffman, D.M. and Weiss, D.M. *Software Fundamentals: Collected Papers by David L. Parnas* New York: Addison-Wesley (2001).Hovde, C. J. et al. *Appl. Environ. Microbiol.* 65, 3233-3235 (1999).