Assessing Aggregate and Cumulative Pesticide Risks Using LifeLine™ Version 1.0

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Assessing Aggregate and Cumulative Exposures to Pesticides Using LifeLine™, A Probabilistic Model

Introduction

Historically, exposure assessors have focused on characterizing the highest levels of exposure that will occur to an individual or a population over time as the result of the use of a pesticide. One approach that is used to characterize the upper bound of exposure is to use simple models of dose rates and a series of conservative model inputs. This approach has great value for screening out exposures that are of little concern. A related approach is to back off from one or more of the "worst-case" assumptions and use a mixture of conservative and more reasonable estimates (US EPA, 1992a). These two approaches form the basis for US EPA exposure guidance such as the draft Standard Operating Procedures (SOPs) for Residential Exposure Assessments (US EPA, 1998).

The difficulty with applying these approaches to aggregate or cumulative exposures is that an individual who receives high levels of exposure from one source will not necessarily receive high levels of exposure from a second or a third source. In fact, there are situations in which exposure to high levels from one source will preclude exposure from a second source. As a result, exposure assessment approaches that focus on defining individuals who have high levels of exposure to a single source cannot be extended to evaluate exposures from multiple sources.

Several solutions have been suggested for this problem. The first is to collect data on the simultaneous exposures of individuals from all sources of exposure to a pesticide for each day of the individuals' life. There are a number of drawbacks to the survey approach. It is difficult to obtain survey results on an individual's behaviors (either food consumption or activity patterns) for periods longer than one or two days. It is also difficult to collect sufficient information on a sufficient number of individuals to allow the evaluation of different subpopulations. Finally, as the number of potential sources increases, the number of behaviors that must be investigated in a survey increases proportionately.

A second approach is to perform biological monitoring and use the individual as an integrator of exposure (ILSI, 1999) Biomonitoring also has its limitations. It requires the availability of analytical techniques for the pesticide or its metabolites in blood or urine. In addition, it cannot be easily applied to new pesticides that are not already in use.

A third approach is to simulate the doses received from multiple sources by individuals in a population. Monte Carlo analysis is often used for these simulations (McKone and Ryan, 1989; McKone and Daniels, 1991). Such simulations have a number of advantages. They can allow the incorporation of data from multiple surveys. Monte Carlo analysis is equally applicable for simple or complex exposure models (Morgan and

Henrion, 1990) allowing the development of simulations that track multiple sources of exposure and multiple pesticides. The technique can be applied to complex time-dependent exposure models that follow individuals through multiple microenvironments (Price et al. 1992, 1996; Keenan et al. 1993; Harrington et al.1995; Goodrum et al. 1996; Muir et al. 1998).

This paper presents an assessment of aggregate pesticide exposures (multiple sources of one pesticide) and cumulative pesticide exposures (multiple pesticides from multiple sources), and their attendant risks, using such a probabilistic model. The model was developed as part of a project (the LifeLine™ project) to develop and widely distribute modeling tools for characterizing pesticide exposure (Price et al. 1999).

Model Description

The LifeLine™ model draws on data from a number of different surveys of exposure-related factors performed in the United States. Information on daily activity and dietary patterns is used to evaluate specific daily exposures for an individual. These data include:

- Natality data ((Birth records) National Center for Health Statistics [NCHS]),
- 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)

In addition, the LifeLine™ model uses the following types of user-supplied information:

- Data on annual or seasonal levels of pesticide residues in agricultural commodities and specific food forms of those commodities (e.g., cooked-canned vs. raw),
- Data on the reduction or increase of residues due to food processing,
- Annual or seasonal data on the fraction of crops that might have been treated with the pesticide,
- The residential uses of the pesticide,
- Physical and chemical properties of the pesticide,

- Frequency and levels of occurrences in ground and surface drinking water supplies,
- Dermal absorption, and
- Toxicity information (NOAEL, uncertainty factors, Food Quality Protection Act (FQPA) factor, and modifying factors) for different durations of exposure[2].

Using these data, the LifeLine™ model defines the exposures to pesticides from dietary residues, residential uses, and contamination of tapwater that occur on each day of an individual's life. These exposures determine the doses that result from the exposures, which are in turn summed to give an estimate of the total or aggregate dose.

The model determines the individual's exposures by modeling where people are born, how individuals grow and age, how they move from home to home and region to region of the US, how they use or do not use pesticides, and their daily activity and dietary patterns. Using chemical-specific information on the fraction of the dermal, oral, and inhalation exposures that are absorbed, the LifeLine™ model calculates the total absorbed dose received from the oral, dermal, and inhalation routes for each day of the individual's life. These estimates of absorbed dose can be summed to give the total systemic (aggregate) dose that can provide the basis for assessing aggregate risk.

Modeling Cumulative Exposure and Risk

Assessments of cumulative risk involve the construction of models of response associated with exposures to multiple pesticides. One such approach, toxicity equivalents, normalizes exposures to a series of chemicals in terms of one standard chemical. The risk from the exposures is then defined in terms of the sum of the toxicity equivalents of the individual chemical (ILSI, 1999). Under this approach, cumulative exposure assessments can be evaluated using LifeLine™.

Modeling Exposures to Dietary Residues

The components of the LifeLine™ model's dietary analysis modules parallel the components of the basic equation used to estimate dietary exposure and the resulting oral dose:

[2] The LifeLine™ model has the ability to evaluate exposure for periods longer than one day. However, such abilities are outside of the scope of this paper.

where:

Dietary exposure is the mass of the pesticide ingested over a period of time from the diet,
Food Item_i is the mass of the ith food item consumed on a given day,
Residue Level_i is the level of the residue in i^{th} food item, and
Oral Absorption[3] is the fraction of the amount of pesticide that is ingested that is absorbed into the blood stream.

The amount of each food item that an individual consumes is taken from the US Department of Agriculture's 1989-91 Continuing Surveys of Food Intake by Individuals (USDA, 1991).

The Residue Level_i is taken from a distribution of residues for each food item. This distribution is generated by the LifeLine™ model based on distributions of residues in the specific Food Forms of the raw agricultural commodities (RACs[4]), the amount of each RAC/Food Form in the food item, and processes that were performed on the RAC (storage, drying, cooking, etc.) during the preparation of the food item.

The amount of each RAC/Food Form combination in a food item reported in the dietary survey is captured in a set of Recipe Files for each food reported eaten in that survey. The Recipe Files in LifeLine™ originates from TAS, Inc., and was made public through US EPA. These files are currently used by US EPA when evaluating the 1989-91 USDA CSFII consumption records[5].

Since the data from the USDA survey and the recipes files are contained in LifeLine™, the user only provides information on the distribution of residues found on treated commodities and/or Food Forms, the percent of each that is treated, and the effects of different processes on the level of residues.

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[3] The value of the oral absorption factor can be influenced by factors such as pesticides affinity for different foods, the pH of the gut, and the volume of food consumed in a meal. Because of the uncertainty in the actual value for this factor a value of 1.0 is typically used in dietary assessments.

[4] The term RAC (for Raw Agricultural Commodity) is used as a category descriptor for all Food Forms of that commodity, whether or not they are raw. Among the common food forms for which separate residue data might be available are Raw, Cooked, Frozen-Raw, Frozen-Cooked, Canned-Cooked, and so forth

[5] The translation files that have been developed for the 1994-96 CSFII consumption records and associated Continuing Survey of Children will be incorporated into future versions of the LifeLine™ model. Those data have been made publicly available by USDA.

Modeling Residential Exposures

Estimates of exposure from residential uses of a pesticide are based on data on pest pressure collected in the National Home and Garden Survey (US EPA, 1992b). This survey determined the frequency with which specific pests required treatment in different residential microenvironments. These data are used, along with user-supplied information on the probability that a product containing the pesticide will be used to treat the pests in the individual's residence, to determine the probability and frequency of using each pesticide in the residence. User-supplied data on pesticide product's characteristics are then used to predict the residues on surfaces and in the air of the residences that result from the use of the pesticide.

LifeLine™ also contains information on the US housing stock, including information on room sizes, air exchange rates and other factors. Using these data and the exposure equations described in US EPA guidance for residential exposure assessments (US EPA, 1998) the model estimates the exposures that occur by the oral, dermal, and inhalation routes. These data are used to estimate the absorbed doses for each route and the aggregate dose. These exposures include both the application-related exposure and the post-application exposures. The post application exposures considered by LifeLine™ include exposures that happen on the day of application and on subsequent days. Table 1 presents the equations used to determine the exposures and doses that occur by the various routes.

Modeling Tapwater Related Exposures

Pesticide residues occur in certain water supplies primarily as the result of agricultural uses of pesticides. When a pesticide occurs in a residence's tapwater, individuals living in those residences will be exposed. The level of exposure will be a function of the level of residues in the water supply. In order to capture the variation in these levels, LifeLine™ allows the input of the distributions of residues that are expected to occur in different types of water supplies. The user can input separate distributions for each of the: four Census regions; urban or rural settings; private wells, public water supplies, or "other water supplies", and each of the four seasons.

Based on mobility data collected by the US government (both the Current Population Statistics and the American Housing Survey) and data on the sources of water for different types of housing stock, the LifeLine™ model tracks the location of the individual's residence in terms of Census region, setting, and source of water. Once the source of the water and the location of the home are determined, a seasonal residue level is assigned to the tapwater of the residence based on the appropriate season-specific distribution.

Once the levels of residues are determined, LifeLine™ uses typical tapwater consumption rates to determine the oral exposure from tapwater sources[6]. The doses associated with the exposures are determined using information on the fraction of the pesticide that is absorbed from the gastro-intestinal tract.

Model Outputs

LifeLine™ generates exposure histories for each of the modeled individuals. These exposure histories consist of route- and source- specific dose estimates for each day in the lives of the simulated individuals. These exposure histories can be mined for information on the intra-individual variation of dose and risk (the variation of dose in one individual's life by age and season) and intra-individual variation in dose and risk (variation in dose across individuals at a specific age and season.) This leads to an important characteristic in LifeLine™ the model is run once and the results are analyzed may times. The LifeLine software includes analysis tools that allow the user to quickly extract information on the inter- and intra- variation in dose in the modeled individuals. This data can be viewed in tabular or graphic form and the data can be exported to Excel, Access, and other software.

One drawback to this approach is the amount of the data that is generated. In order to avoid generating files that could overload older computers and that would be difficult to access because of their size. Version 1.0 calculates but does not save the dose estimates for each day. This results in large reduction in the size of the output files.

Because exposures to pesticides vary with the age of the individual and season of the exposure it is important that the software save data on exposures for each year and season. It is also useful to look at the average and the maximum doses an individual receives on any day of a given season and year of his or her life. Therefore LifeLine™ model determines the **average exposure for each year and season** and the **maximum dose that occurs on any day in a season for each year and season**, see Figure 1.

The average seasonal dose is useful in comparing the doses to the typical individual in the modeled population. This measure has been used to investigate how the typical aggregate and cumulative doses in the simulated population vary by age and season. The maximum dose is useful in determining the upper bounds of the distribution of doses that occur to individuals. All results presented in this paper are based on either the mean daily dose for a season or the maximum daily dose seen on any given day during a season.

Modeling Aggregate Risks

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[6] The LifeLine™ model also determines doses from dermal exposure to tapwater components and inhalation exposures to any pesticides that may volatilize from tapwater. A complete discussion of these routes of exposure is beyond the scope of this paper.

Assessing Aggregate and Cumulative Exposures to Pesticides Using LifeLine™, A Probabilistic Model

As discussed above, the LifeLine™ model determines the route-specific exposures received by a specific individual at a specific time and place[7]. These estimates of exposure are used to determine the absorbed dose associated with each route's exposure. These route specific doses are summed to give the aggregate dose. This dose is then used to evaluate aggregate risks. As a result, portal effects are not considered in the evaluation of aggregate risks. Such effects should be evaluated in a separate analysis.

Modeling Cumulative Risk

In this study, we evaluate the cumulative risks from concurrent daily exposures to multiple pesticides operating by a common mechanism using a relative toxicity potency (RTP) model. Under this approach, the pesticides being modeled are assumed to have additive effects and the effect of each chemical can be defined in terms of an equivalent dose of a single index chemical.

In the case study described below we investigate three hypothetical pesticides Alpha, Beta, and Gamma. In his study, Alpha is used as the index chemical and the doses for Beta and Gamma are converted to toxicologically equivalent doses of Alpha by the application of relative toxicity factors (RTFs).

One of the commonly used risk metrics for the evaluation of noncarcinogenic risk is the percent reference dose (%RfD). Using the RTP model the cumulative risk for three pesticides, Alpha, Beta, and Gamma, the risk metrics would be calculated using the following equations:

Where:

[7] The LifeLine™ model is thus internally consistent in the time frame and geographical scale.

PAD is the population-adjusted dose. For children and women of child bearing age the PAD is defined as the reference dose (RfD) divided by the FQPA factor. For all other ages it is equal to the RfD.
Alpha, Beta, and Gamma are the doses of the three compounds.
TEQ_{Alpha} is the toxicity equivalent dose for Alpha and is equal to the dose of Alpha.
TEQ_{Beta} is the toxicity equivalent dose for Beta and is equal to the dose of Beta times the RTF for Beta (RTF_{Beta}).
TEQ_{Gamma} is the toxicity equivalent dose for Gamma and is equal to the dose of Gamma times the RTF for Gamma (RTF_{Gamma}).

Case Studies of Aggregate and Cumulative Exposure

This paper includes two applications of the LifeLine™ model. The first is a characterization of the aggregate risk associated with one-day exposure to a single pesticide, Alpha. The second application is the characterization of the aggregate risks from two pesticides Beta and Gamma and the cumulative risks from the concurrent daily exposure to three pesticides, Alpha, Beta, and Gamma[8].

Cumulative exposures are determined using an approach similar to that used to assess aggregate exposures. In the case of dietary exposures, data on the co-occurrence of the residues of the pesticides in a food are converted to TEQs for an index chemical (in this case Alpha) and summed to give a distribution of TEQs for that food. These distributions of TEQs can be entered into LifeLine™ as if they were the concentrations of a single compound.

A similar approach is used for the evaluation of tapwater exposures. Data on concurrent levels of pesticides measured in surveys of water supplies are converted to a single distribution of TEQ and entered into the LifeLine™ model.

A somewhat different approach is used in the assessment of residential sources of exposures. For these sources of exposure, the amounts of each of the three pesticides applied during the use of a specific product are converted to the corresponding TEQs. Then LifeLine™ is run with all of the products that contain any of the three compounds.

As with the first study, exposures to any of the three pesticides (expressed as TEQs) from all sources are determined for each day for each of the simulated individuals. The estimates of cumulative dose (in TEQs) can be determined by summing doses from each route of exposure.

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[8] The compounds were chosen to illustrate the properties and uses of pesticides currently in use. However, the compounds are not meant to represent any specific pesticide.

Model Inputs

Assessing Risks from Aggregate Exposure

The first application is of a hypothetical pesticide, Alpha. Alpha is used in products that control pests on apples[9]. Table 2 presents the residue data for Alpha on apples that were collected in a market basket survey. Alpha is also used in two residential pesticide products. The first, Alpha-pump, is a pump spray applied as a crack and crevice treatment in homes. The second, Alpha-gran, is a granular product that is applied to turf using a drop spreader. Table 3 summarizes the data for these two products.

The agricultural uses of Alpha contaminate surface waters used for drinking water supplies in areas of the southern portion of the United States. This contamination largely occurs during spring application of the products. Levels are below the detection limit during the other seasons. Table 4 presents the cumulative distribution of Alpha residue levels for the population living in this region and using surface water supplies in the spring. The levels during the other seasons are assumed to be equal to one half of the detection limit (0.005 ug/l).

Alpha has been found to be well absorbed by the oral and inhalation routes and partially absorbed by the dermal route. The values for dermal absorption, lung clearance, and GI absorption are 0.03, 1.0, and 1.0. Table 5 presents the information on the acute noncarcinogenic effects of Alpha and the toxicological factors established for the compound.

Assessing Risks from Cumulative Exposures to Three Pesticides

The second application estimates the cumulative risks from exposures to Alpha and two additional hypothetical pesticides Beta and Gamma. Beta and Gamma have been determined to cause adverse effects by mechanisms similar to that of Alpha. Values for Beta's and Gamma's RTFs are set using the ratio of the compounds' NOAELs to the NOAEL of Alpha[10]. Using the data in Table 5, a RTF of 0.5 has been determined for Beta and a RTF of 2.0 has been determined for Gamma.

Beta is used on apples and on wheat. Table 2 gives information on the concurrent levels of Beta found in the same market basket survey as Alpha. The data on the concurrent levels have been used to estimate the cumulate level of the pesticides in units of TEQ. Table 2 also presents the estimates of TEQs for the mixtures of the two pesticides. The levels in wheat were taken from field trials. Beta is used on all wheat (percent crop treated equal 100%). Gamma is used in one residential product, Gamma spray. Table 3

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[9] For simplicity sake we do not address the issues of food processing factors or bioaccumulation of pesticides in beef and dairy products.

[10] Other approaches for setting RTF could be used.

gives the data on this product. The amount of Gamma applied and the air levels are expressed in terms of mass of TEQs. The two compounds have absorption characteristics similar to those of Alpha[11].

Model Operation

The LifeLine™ model was run with the data on Alpha and with the data on all three compounds. The LifeLine™ model runs were performed on a PC with a Pentium III 700 MHz using Windows 2000. The model runs simulated exposure histories for 2,000 individuals. Different dietary and activity patterns records were selected for each day of each season (Price et al., 1999). The lengths of time necessary to run the model range from 30 minutes to overnight depending on the number of years that were modeled.

Results

Results of Study 1 –Aggregate Risks

Figure 2 presents the results from each source of pesticide exposure (diet, residential, and tapwater) and the aggregate (or total) daily dose for each year and season of the 2,000 individuals. The dose presented is the mean of each individual's mean daily dose over each season and age. This figure provides insight into the age and seasonal patterns of exposure and the relative contribution of each route to the total dose for the typical individual. The measurements are in units of mg/kg/day of absorbed dose.

Figures 3 and 4 present the distributions of the interindividual variation in the population's aggregate doses at two combinations of age and season, 3 year olds in winter and 35 year olds in winter. The doses for each individual appear on the same vertical line. The doses presented are the highest daily dose seen by each individual on any day during the season from tapwater, residential use, and dietary sources and the aggregate dose from all sources.

The data for doses have been ranked from the lowest to the highest aggregate dose. The aggregate doses of each individual are presented as gray squares. Because of the number of individuals, these gray squares appear a gray band. The relative importance of a source can be seen by the vertical distance between a symbol of a route specific dose and the band of gray squares (the aggregate doses). Routes that are the dominant contribution to an individual's aggregate dose will have a symbol that appears close to or directly on top of a gray square. Routes that make minimal contributions appear some distance below the gray squares.

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[11] The current version of LifeLine™ uses the same set of route specific absorption factors for all three pesticides. Future versions of LifeLine™ will allow the user to specify compound-specific factors.

Figure 5 presents the %RfD associated the aggregate doses of simulated population when the individuals for the same ages/seasons. This figure indicates that approximately 10% of three year olds had %RfDs in excess of 100 for at least one day during that season while none of the 35 years old had %RfDs in excess of 100 on any of the days.

Results of Test Case 2

Figure 6 presents the aggregate doses of Alpha (also presented in Figure 1) and the cumulative doses for exposures to all three compounds in mg TEQ/kg/day for each season and year of the modeled individual's lives. As with Figure 1, the measures of dose are the averages of the seasonal average of the daily dose for each of the 2,000 individuals for each day of a season/age.

Figure 7 presents a cross section of the population's cumulative doses of Alpha, Beta, and Gamma during winter at age 3. The doses presented are the distribution of the highest daily total dose seen by each individual on any day during the season. The figure also presents the aggregate doses of the individual pesticides. These data were produced by separate analyses. Thus the data sets (unlike those in Figures 3 and 4) do not reflect data on the same individuals. All four distributions have been independently ranked by size.

Figure 8 presents the %RfD associated the aggregate dose of Alpha and the cumulative doses of Alpha, Beta, and Gamma for three year olds in winter. This figure indicates that approximately 10% of three year olds had %RfDs in excess of 100 from exposure to Alpha for at least one day per season and the fraction with %RfDs increased to 16% when the cumulative risks were determined.

Discussion

The results of the modeling are a function of the specific assumptions developed for the three hypothetical pesticides and may not apply to other compounds. However, the results demonstrate how the LifeLine™ model can give insights into the doses and associated risks that result from the exposure to each pesticide both singly and cumulatively.

The results of the model runs presented in Figure 2 suggest that magnitude of the average daily aggregate dose in a season and the sources of those doses for the modeled pesticides are strongly affected by age and to a lesser extent by season. The largest doses occur to children and occur from exposures to residential sources. After age 6 the dominant source of the average daily aggregate dose is dietary exposures. Tapwater exposures do not make a significant contribution at any age. The limited effect of

Tapwater occurs in part because this source affects such a small portion of the population.

The dietary and tapwater sources of pesticide exposures for Alpha vary by season. This can be seen in the cyclical pattern in the estimates of dose from each source in Figure 2. The seasonal variation in the tapwater is driven by the seasonal nature of tapwater contamination, see Table 4. The seasonal variation in diet is created by the seasonal pattern of consumption (more apples are consumed in the fall and winter than in spring and summer).

Figures 3 and 4 indicate that all of the simulated individuals have at least some exposure to Alpha on at least one day of the winter season when they were aged 3 and 35. This is the probable result of Alpha residues being found in apples, which either directly (raw) or as a component of food forms (juice, pies, pastries, etc.) occur in many individual's diets. The range of maximum seasonal dose is quite large, ranging about three orders of magnitude across the population. As would be expected, the dietary doses for the 3 year old children are higher than the doses for the 35 year old adults.

The sources of exposure are for the highly exposed portions of the populations differ in the two age groups. For the three year olds, the top 10% of aggregate doses occur in individuals whose aggregate doses are dominated by residential exposures. In the 35 year old's, the top 10% of the population includes individuals whose aggregate doses are dominated by both residential and dietary sources.

In both Figures 3 and 4, the symbol for the dose from one of the routes (a circle, triangle, or x) falls almost directly on top of symbol for total dose (a gray square). This indicates that the total dose is almost entirely the result of the dose received from one of the sources of exposure (usually diet or residential).

In Figure 5, the aggregate doses for Alpha for 3 year olds in winter result in %RfDs that are greater than 100 (for at least 1 day per season) for about 10% of the population. A comparison of Figures 3 and 4 demonstrates that both residential and dietary sources resulted in individuals having %RfD values greater than 100. In contrast none of the thirty five year olds have doses that result in values of % RfD that are greater than 100. This difference is due to the lower doses in adults and because the FQPA factor is applied to both male and female three year olds but only to female 35 year olds.

Figure 6 presents a comparison of the average cumulative doses of Alpha and the average aggregate doses for the three pesticides. As the figure indicates, the patterns are similar with the cumulative doses expressed in TEQs typically about two fold higher than the aggregate doses of Alpha.

Figure 7 presents the distribution of interindividual variation cross section of the population's cumulative doses of the three pesticides as well as the aggregate doses for each of the pesticides during winter at age 3. All doses are expressed in units of mg TEQ/kg/day. The figure demonstrates that exposures to Gamma are limited to a small fraction of the population. This limitation occurs because not all 3 year olds will reside in houses where Gamma is used. In contrast, almost all three year olds had some level of exposure to Alpha and Beta because of the use of the compounds on wheat and apples. The cumulative doses at the upper end of the distribution are about 1.3-1.9 fold lower than would be estimated if the corresponding percentiles of the distribution of Alpha, Beta, and Gamma were simply added together.

This lack of additivity occurs because the individuals receiving higher doses are exposed from residential sources. The LifeLine™ model assumes that if a residence uses a pesticide containing Alpha to control a pest, then a pesticide containing Gamma is not being used to control that pest on that day. Thus, the daily exposure will be driven by one pesticide or the other but not both.

Figure 8 presents the MOE and %RfD associated the aggregate dose of Alpha and the cumulative doses of Alpha, Beta, and Gamma for three year olds in the winter. This figure indicates that approximately 10% of three year olds had %RfDs in excess of 100 from exposure to Alpha for at least one day per season and the fraction with %RfDs increased to 16% when the cumulative risks were determined. Thus the net effect of considering cumulative risk was an increase of 6% in a potential population of concern.

Because figures 3, 4, 5, and 8 present the distribution of the maximum dose that occurs on any day of the season the doses will be much higher than the average daily doses for the season (given in Figures 2 and 6). For example, the aggregate dose of Alpha for the average 3-year old on an average winter day is 0.00062 mg/kg/day. In contrast the mean dose in the distribution of the maximum seasonal doses is 0.0030 mg/kg/day a value six fold higher.

Conclusions

Version 1.0 of LifeLine presents a number of useful capabilities in the assessment of aggregate and cumulative risk. First, the model give the assessor the ability to estimate exposure and risks as a function of age and season across individual's lifetimes. This ability comes from the model's design that tracks the exposure to the <u>same</u> modeled individuals at different ages. This ability allows the assessor to focus attention on those periods where exposure and concerns are highest.

Second, the assessor has the ability to determine the source of exposure that has the greatest impact on the exposures to the typical and highly exposed portions of the population. In this study residential use affect only a small portion of the population but was found to be the dominant source of aggregate risk for Alpha and cumulative risk for the mixture of Alpha, Gamma, and Beta.

Finally, the model gives the assessor the ability to determine the inter-individual variation in dose and risk across individual of any age and in any season. This type of data offers the ability to determine the fraction of the population that exceeds a risk or exposure criterion for age and season.

While the three chemicals used in this demonstration case are hypothetical chemicals, the chemical characteristics and use profiles are similar to a number of pesticides. The analyses, therefore, present results that may be similar to those that would occur in analyses of actual compounds. Although we cannot use this demonstration case to make generalizations about the risk of any particular pesticide or classes of pesticides, the characteristics of such assessments provide important lessons.

First, age-related exposure profiles are likely to be a vital component of a risk assessment. Identifying the periods of high exposure and the contributors to those periods of exposure are necessary elements of the risk assessment process. For example, in the demonstration case children's exposures were higher than adult's and the average winter exposures were higher than summer exposures. Other assessments may find other patterns of variation in age and seasonal exposures.

Second, the case study found that when sources of pesticides are independent, the average dose that occurred to a population in a season and age was roughly additive. that is the average aggregate dose was approximately equal to the sum of the average doses from each source. However, the maximum seasonal aggregate exposures tended to be equal to the dose from the highest single route of exposure. That is the maximum aggregate dose was dominated by the dose from one route.

Third, cumulative exposure in this study could not be predicted by simply adding the dose equivalents for corresponding percentiles of the dose distributions for each of the three pesticides. The addition of the doses in the corresponding percentiles tended to overestimate risks to the most highly exposed individuals. This occurs even when multiple pesticides are used on the same crop and to control the same residential pests. This finding may not hold true when the pesticide applications are not independent (as with pesticides that are applied as a mixture). Such use profiles were not considered in this case study and should be explored in future analyses.

Finally, certain sources affect all individuals in a population while other sources only affect a small subpopulation. As a result, cumulative plots of interindividual variation in

aggregate and cumulative doses will typically appear as a series of steps and the frequency distribution of such doses (not shown) will be multi-modal.

In summary, this paper demonstrates that probabilistic models such as LifeLine™ using existing data can characterize both cumulative and aggregate exposures to pesticides. The LifeLine™ model can be used to identify the critical sources of exposure and the influence of factors such as age and season. For example, the findings in this analysis suggest that the reduction of risks from these three hypothetical pesticides should focus on the residential sources of exposure.

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Table 1. Equations Used to Evaluate Daily Residential Exposures and Dose

Where:

$Air_Concentration_i$: average concentration of a pesticide in the air of the ith microenvironment.
$Inhalation_Rate_i$: inhalation rate of the Modeled individual in the ith microenvironment.
$Duration_i$: length of time spent in the in the ith microenvironment.
Lung_Clearance: fraction of the inhaled pesticide that is absorbed and is added to the individual's systemic dose.
$Dislodg_Res_i$: concentration of pesticide per unit area that can be removed by dermal contact.
$Dermal_Transfer_Factor_i$: rate of transfer of pesticide from surfaces to the individual's skin in the in the ith microenvironment.
Fraction_Absorbed: fraction of the pesticide on the skin that is absorbed and is added to the individual's systemic dose.
Incidental_Oral_Exposure: the ingestion of pesticide that occurs when a portion of the hand is placed in the mouth.
Soil Ingestion: the rate that an individual ingests soil.
Grass Ingestion: the rate that an individual ingests grass.
GI_Absorption: fraction of the ingested pesticide that is absorbed and is added to the individual's systemic dose.
$Events_i$: frequency that an individual places a portion of their hand in their mouth in the ith microenvironment.
$Hand_Fract_i$: fraction of the individual's hand placed in the mouth when in the ith microenvironment.
$Refresh_i$: ratio of the average amount of residue on the hand to dislodgable residue (refreshment fraction) when in the ith microenvironment.
Saliva Extraction: fraction of pesticide on the hand that is extracted by saliva.
Soil Ingestion: amount of soil ingested per unit time.
Soil Residue: amount of pesticide in soil.
Grass Ingestion: amount of grass ingested per unit time.
Grass Residue: amount of pesticide in grass.

Table 2. Measurements of Concentration of Alpha and Beta in Samples Take in a Market Basket Survey

	Apples			Wheat	
Samples	**Alpha (ppm)**	**Beta (ppm)**	**Cumulative (ppm TEQs)**	**Beta (ppm)**	**Cumulative (ppm TEQs)**
1	0.008	0.010	0.013	0.005	0.0025
2	0.005	0.005	0.008	0.005	0.0025
3	0.005	0.019	0.015	0.005	0.0025
4	0.005	0.420	0.215	0.005	0.0025
5	0.027	0.005	0.030	0.005	0.0025
6	0.021	0.083	0.062	0.005	0.0025
7	0.005	0.007	0.008	0.005	0.0025
8	0.005	0.005	0.008	0.005	0.0025
9	0.005	0.005	0.008	0.010	0.005
10	0.005	0.363	0.186	0.014	0.007
11	0.028	0.005	0.030	0.091	0.046
12	0.005	0.005	0.008	0.005	0.0025
13	0.005	0.043	0.026	0.005	0.0025
14	0.005	0.005	0.008	0.005	0.0025
15	0.005	0.006	0.008	0.005	0.0025
16	0.005	0.078	0.044	3.990	1.995
17	0.005	0.005	0.008	0.005	0.0025
18	0.005	0.005	0.008	0.791	0.396
19	0.059	0.005	0.062	0.041	0.021
20	0.005	0.005	0.008	0.005	0.0025
21	0.005	0.005	0.008	0.005	0.0025
22	0.005	0.005	0.008	0.005	0.0025
23	0.005	0.005	0.008	0.005	0.0025
24	0.005	0.005	0.008	0.005	0.0025

Table 3. Data on Residential use of Alpha and Gamma			
Product	Alpha-pump	Alpha-gran	Gamma-spray
Application Method	Trigger Sprayer / Crack and Crevice	Drop-spreader / Granular	Aerosol/Broadcast
Location of Use	Indoors	Yard (Turf)	Indoors
Application rate of product	1500 mg/m	30,000 mg/m^2	1,000 mg/m^2
Concentration of AI in product (as applied)	0.5%	0.5%	0.8% (by Weight) 1.6% (TEQs)
Peak Air Concentration	0.01 mg/m^3	--[1]	0.01 mg/m^3 (by Weight) 0.02 mg/m^3 (TEQs)
Percent daily dissipation on hard surfaces	20%	--	15%
Percent daily dissipation on carpeted surfaces	10%	--	8%
Percent daily decline in dislodgable mass from turf	--	20%	--
Percent daily dissipation on turf	--	10%	--
Percent daily dissipation in soil	--	10%	--
Fraction Dislodgable on hard surfaces.	0.10	--	0.10
Fraction Dislodgable on soft surfaces.	0.02	--	0.02
Fraction Dislodgable on Turf	--	0.05	--
Dermal Unit Exposure ng/lb AI	2,400,000	6,300	1,200,000
Inhalation Unit Exposure ug/lb AI	220,000	2,900	500,000
Pests Controlled	Ants, Roaches, Fleas, Spiders	Soil dwelling insects	Ants, Fleas, Spiders
Market share (for all pests)	50%	30%	20%
Minimum repeat time	7 days	60 days	14 days

[1]Not applicable

Table. 4 Cumulative Distributions for Measured Levels of Alpha in Surface Water Supplies in the Southern Region of the US During Spring

Percentile	Concentration of Alpha (ug/l)
0	0.0
0.70	0.00
0.75	0.005
0.85	0.05
0.97	0.1
0.985	0.5
0.9925	1.0
0.997	1.25
1.0	1.5

Table 5. Toxicity Data for Alpha, Beta, and Gamma				
	Oral	Dermal	Inhalation	Systemic
Short-term NOAEL				
Alpha	5 (mg/kg-d)	5 (mg/kg-d)	5 (mg/kg-d)	5 (mg/kg-d)
Beta	10 (mg/kg-d)	10 (mg/kg-d)	10 (mg/kg-d)	10 (mg/kg-d)
Gamma	2.5 (mg/kg-d)	2.5 (mg/kg-d)	2.5 (mg/kg-d)	2.5 (mg/kg-d)
Uncertainty Factor (All Compounds)	100	100	100	100
Modifying Factor (All Compounds)	1	1	1	1
FQPA Factor (All Compounds)	10	10	10	10

Assessing Aggregate and Cumulative Exposures to Pesticides Using LifeLine™, A Probabilistic Model

Legends for Figures

Figure 1.

Daily doses for one season in an individual's exposure history. While each day's dose is calculated, only the average dose and the maximum dose are retained as outputs.

Figure 2

Average daily doses of Alpha by age and season for the modeled population. The doses include the average dose for tapwater, diet, and residential sources as well as the total (aggregate) dose for all routes.

Figure 3

This figure presents each individual's total (aggregate) dose and the dose from tapwater, residential and dietary sources during winter for individuals aged three. The data for each individual has been ranked according to total dose. For almost all of the individuals the total dose is dominated by one source of exposure. Thus the symbol for the dominant source specific dose falls close to or on top of the symbol for aggregate dose. Residential exposure is the dominant source for individuals with high aggregate doses.

Figure 4

This figure presents each individual's total (aggregate) dose and the dose from tapwater, residential and dietary sources during winter for individuals aged thirty five. The data for each individual has been ranked according to total dose. Both diet and residential are dominant sources for individuals with the high aggregate doses.

Figure 5

Estimates of %RfD for the 2,000 modeled individuals at ages three and thirty five during winter. Estimates have been separately ranked. Approximately 10% of the three year olds have % RfD that are greater than 100. None of the thirty five year olds have %RfD that are greater than 100.

Figure 6

Average aggregate dose of Alpha and average cumulative dose of Alpha, Beta, and Gamma by age and season for the modeled population. Units of dose are in mg of the index chemical (Alpha).

Figure 7

This figure presents the maximum seasonal aggregate doses of Alpha, Beta, Gamma and cumulative dose of all three pesticides during winter for individuals aged three. All four dose distributions have been ranked separately. Units of dose are in mg of the index chemical (Alpha).

Figure 8

This figure presents the %RfD associated with each of 2000 Modeled individual's aggregate exposures to Alpha and cumulative exposure for Alpha, Beta, and Gamma in three year olds during winter. Both distributions are ranked separately.