

Appendix I

EXAMPLE CALCULATIONS
(Food, Water; Aggregate and Cumulative)

February 1, 2002

Revised Draft

Introduction

This Appendix is an accompaniment to the paper, "Status of Cumulative Risk Assessment for Organophosphate Pesticides," dated January 15, 2002. As explained in that paper the purpose of the entire guide is to assist the reader by identifying and explaining the key features of the OP cumulative risk assessment. Because the assessment is preliminary, some elements may change before release of the revised assessment. Changes are possible as a result of the public comment period on the preliminary risk assessment; review by the FIFRA Scientific Advisory Panel scheduled for February 2002; as well as continuing work by the Agency.

In this Appendix OPP has developed example calculations to help explain how a Monte Carlo analysis might be conducted for three types of risk assessment: food alone, partial aggregate (food & water), and cumulative (food & water/multiple chemicals). The goal of the examples provided here is to give a level of detail that is appropriate for non-specialists to better understand the components of the risk assessment and the methods and assumptions that it involves.

- ❖ Any risk assessment uses data and must rely on certain assumptions. To understand the results of the assessment, one must review the data and the assumptions that underlie the assessment. This information is provided with the assessment when it is released.
- ❖ OPP uses computer software programs to generate the assessments. The program that OPP is currently using to generate the OP cumulative assessment, Calendex™, has been reviewed by the FIFRA scientific Advisory Panel. The details of how it operates, including critical portions of the computer code, are publicly available.

Monte Carlo Analysis

Monte Carlo analysis is one of several mathematical techniques for performing probabilistic assessments. The method relies on the computational powers of modern computers to estimate the range and frequency of all possible outcomes of a process based on repeatedly simulating that process by sampling from the inputs provided by the analyst. These inputs are combined according to the model that is specified by the analyst. Thus, for example, to assess the entire range of possible food exposures to pesticides, and their probability of occurrence, would require:

- specification of a model that combines food consumption and pesticide residues on that food, and
- provision of input values for pesticide residues and consumption.

Once the computer software is provided with the necessary inputs, it will generate the output as a distribution of all possible exposures by repeatedly sampling from the inputs and combining these inputs according to the model. Whether this output distribution is an appropriate representation of the distribution of exposures in the real world depends on:

- how well the model represents the actual processes in the real world, and
- the accuracy, or representativeness, of the inputs into the model.

In an attempt to simplify the discussion, the example calculations have been divided into several parts and this Appendix addresses only food and water, not residential exposure.

- I. Food; one chemical; one day
- II. Food & water; one chemical; one day
- III. Food & water; multiple chemicals; one day
- IV. Multiple days

In “building” an assessment such as this OPP would not necessarily perform each of the “steps” in the sequence illustrated here. Nevertheless, we believe that illustrating the process in this way is beneficial in that it considerably simplifies the explanation. In particular, the examples begin with an exposure analysis for a single day. This is not because a single day analysis would necessarily be performed, but because the single day exposures serve as the building blocks for development of any longer term exposure of interest.

For each step discussed below, the critical pieces of the Monte Carlo analysis--the input files and the model used to combine the inputs--will be examined in some detail. The example in each section shows how these input files may be combined using the model specified for that type of assessment.

V. Food; One Chemical; One Day

Inputs

Food exposure estimates are derived from two distinct pieces of information:

- the amount of pesticide residue that is present in and on food (i.e., the residue level) and
- the types and amounts of food in a person's diet (i.e., food consumption).

The residue information comes mainly from chemical specific monitoring data collected by the USDA and FDA or, when these are not available, from the crop field trials submitted by pesticide manufacturers and USDA. The preliminary OP cumulative assessment relies on available monitoring data. Consumption information comes from USDA surveys of what people eat. These input data are described in detail below.

(1) Food Consumption: USDA Continuing Survey of Food Intake by Individuals

The primary source of food consumption data used in dietary risk assessments is the Continuing Survey of Food Intakes by Individuals (CSFII). The CSFII is particularly well suited for national-level dietary risk assessments because it is statistically designed to sample individuals of all ages and ethnicities to accurately reflect national demographics. It is also balanced so that all seasons of the year and the major regions of the country are represented.

The food survey data being used in the preliminary OP cumulative risk assessment were collected by the U.S. Department of Agriculture in the 1994-96 surveys and the 1998 Supplemental Children's Survey. Together, these surveys are referred to as the 1994-96/1998 CSFII.

The 1994-96 CSFII was conducted as three separate one-year surveys in 1994, 1995 and 1996. The 1998 survey (the Children's Supplemental Survey) was designed to be combined with and supplement the 1994-96 survey. It concentrated on children aged from birth to nine years old. The supplemental survey greatly expanded the number of children included in the survey, increasing the number of survey participants in many sub-age categories by four- or five- fold.

USDA has been conducting these food surveys since the 1930s by means of personal interviews in which interviewers ask individuals to recall everything they ate and drank over the previous 24 hours.

- CSFII (1994-96/1998) data are derived from information provided by thousands of individuals who participated in the survey.
- Two (non-consecutive) days of food and nutrient intake data for individuals of all ages were collected by personal in-home interviews.

The data collected for such large numbers of survey participants, who have been scientifically selected so that results could be projected from the sample to the U.S. population, constitute a reliable and representative national sample.

(2) Residue Data Sources

For the preliminary OP cumulative risk assessment data on the residues of pesticides in foods were obtained mainly from the USDA's Pesticide Data Program (PDP) supplemented with information from the Food and Drug Administration (FDA) Surveillance Monitoring Program and Total Diet Study. Data from PDP are EPA's principal source of monitoring data for use in assessing risk from exposure to pesticide residues in food.

- PDP pesticide monitoring activities are a federal-state partnership. Ten participating states, which represent about 50 percent of the nation's population and all regions of the country, collect samples of fruits, vegetables, and other commodities.
- PDP's statistically-reliable sampling protocol is designed to select random samples that best represent pesticide residues in the food supply to allow for a realistic estimate of exposure. The sampling protocol was developed in cooperation with the Agency and the data generated are specifically designed to be used for risk assessment. Fresh agricultural products and processed foods are widely distributed, therefore, it is assumed that each person has the same probability of being exposed to any given residue.
- Samples are collected close to the point of consumption—at terminal markets and large chain store distribution centers immediately prior to distribution to supermarkets and grocery stores. They take into account pesticide degradation during transit and storage, and provide data on residues resulting from post-harvest applications of fungicides and growth regulators.
- The number of samples collected is determined by the state's population or commodity turnover information.

- Samples are randomly chosen without regard to commodity origin or variety. They reflect what is typically available to the U.S. consumer throughout the year.

A detailed discussion of the available FDA data and how they were used in the preliminary OP cumulative risk assessment is contained in the accompanying paper.

EPA also, in some cases, uses measured residue data from one commodity to represent residues on a similar commodity for which measured residue data are not available. For example, residue data for cauliflower might be used for broccoli if the pesticide use pattern is similar. This procedure is called “translation” of data. This process is discussed in the accompanying paper.

OPP uses DEEM™, the food component of the Calendex™ software, for all of its food risk assessments. The following review of how DEEM™ works will assist with understanding how EPA conducts the aggregate (only food and water in this Appendix) and cumulative (multiple chemicals) risk assessments using Calendex™.

The two major inputs into the food exposure assessment are information on what food is eaten by representative individuals and in what quantity; and information on pesticide residues estimated to be on that food. The consumption information includes exactly what each individual ate as well as demographic information (e.g., age, sex, weight) on each individual. The residue files contain information on the residues expected on food. Estimates of resulting exposure (which represents the combining of data on food consumed with pesticide concentrations in those foods) are generated for the general U.S. population and specific sub-populations (e.g., children) using the demographic and other information available for each individual in the CSFII survey. In addition, self-reported body weight is used to convert exposure in milligrams (mg) of pesticide per day into mg of pesticide per kilogram (kg) of body weight per day, so that it can be compared to a toxicological endpoint expressed in mg of pesticide per kg of body weight per day.

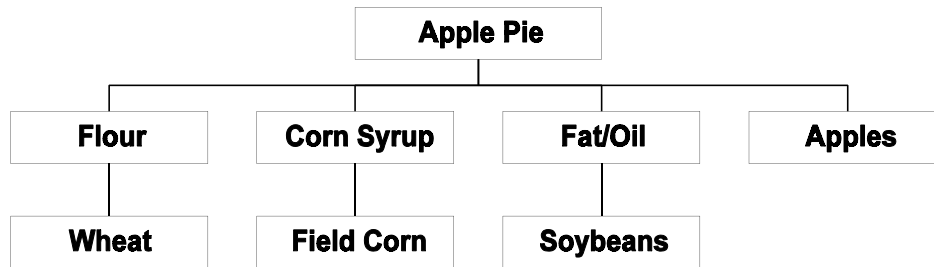
Preliminary Steps

Consumption Data Adjustments

Respondents in the CSFII survey report what they ate in the form the food was eaten (e.g., apple pie). DEEM™ includes recipes and

formulas that allow it to convert these foods to their components (e.g., apples, wheat, field corn, etc.), since residues are measured on these components. Using a very simplified example, the reported consumption of “apple pie” might become four components or food forms (apples, wheat, field corn, and soybeans) for which residue data are available. The actual recipes account for many more ingredients than illustrated here. The following diagram illustrates this process.

Figure 1



In addition to breaking down “as eaten” foods into their components, the recipes include the quantity of each ingredient. The following table shows the results of this conversion process for one hypothetical person’s diet for one day.

**“Agricultural Commodity Form”
of Person #1's Day 1 Diet**

<u>Food or Food Form</u>	<u>Grams Consumed</u>
apples	40
wheat	30
field corn	3
soybean	1
carrots (cooked)	25
milk	20

For each person in the CSFII who has complete two day records of food consumption, DEEM™ converts each day’s food consumption as illustrated above.

Residue Data Adjustments

The residues may be adjusted to more closely reflect the residues

that may actually be consumed. These adjustments may include, for example, accounting for residue changes resulting from cooking and processing and deciding how to handle such issues as non-detectable residues and “blended” commodities such as grain.

The following discussion illustrates the concepts behind the adjustments for cooking and processing. Note that other types of adjustments are possible. Adjustments for cooking and processing are made to account for the fact that residues are not necessarily measured on the food in the same form that the food is consumed. Data may be available that show how various types of processes affect residues. For example, residues can be reduced as the result of washing, peeling, and cooking food. Residues may be concentrated by some processes, such as drying. Data are often available which result in “factors” that describe the change in residues from a particular processing method.

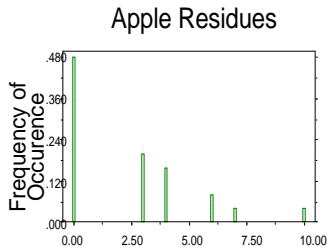
For example, assume Person #1 reports eating cooked carrots. The available residue data reflect raw carrots, but a processing factor is available showing the effect of cooking on carrot residues. Therefore, the residues for raw carrots will be adjusted using the cooking factor to create a new residue file for the food form cooked carrots. This file will reflect the reduction in the residues on raw carrots that results from cooking. DEEM™ will then look in this residue file when selecting a residue value for cooked carrots.

Because the OP cumulative assessment relies only on monitoring data, the adjustments for cooking and processing are the only major adjustments that were made to the residues. However, depending on the type of analysis being done and the residue data being used, other adjustments of the residues may be made.

After all of the residue files have been adjusted, as appropriate, and files have been developed for all of the foods and food forms necessary for the assessment, the result is a universe of residue files, one for each food or food form. The residue values may look like the following:

Apples

Graphically:

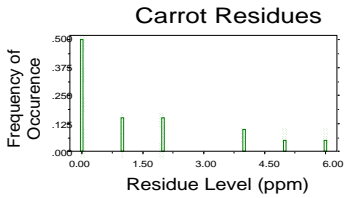


DEEM™ 3 ppm 4 ppm 10 ppm
Sees as
a List of
Residue
Values: 3 ppm 4 ppm
 3 ppm 6 ppm
 3 ppm 6 ppm
 4 ppm 7 ppm

and 12 residue values
of 0 ppm

Carrots, Cooked

Graphically:



DEEM™ 1 ppm 4 ppm
Sees as
a List of
Residue
Values 1 ppm 4 ppm
 1 ppm 5 ppm
 2 ppm 6 ppm
 2 ppm
 2 ppm

and 10 residue values
of 0 ppm

etc. , For All of the Foods and Food Forms in the CSFII

Illustrated below is an actual DEEM™ file, with the elements discussed above.

NOTE

Totalnz = the number of residue values that are NOT equal to zero—10 in this case. They are listed in the file below.

Totalz = the number of residue values that are zero – 10 in this case – meaning that in 50% of the Monte Carlo iterations zero is chosen as the residue value

Carrots
totalnz=10
totalz=10

1
1
1
2
2
2
2
4
4
5
6

Apples
total nz=13
total z=12

3
3
3
3
3
4
4
4
4
4
6
6
7
10

NOTE

Totalnz = the number of residue values that are NOT equal to zero—13 in this case. They are listed in the file below.

Totalz = the number of residue values that are zero – 12 in this case – meaning that in slightly less than 50% of the Monte Carlo iterations zero is chosen as the residue value

Fresh agricultural products and processed foods are widely distributed, and are assumed to be “national” commodities. Therefore, in the analysis the same residue files are used for every person.

Exposure Calculations

The following relationship is used to combine consumption and residue information to estimate exposure:


$$\text{Exposure} = \text{Consumption} \times \text{Residue}$$

The calculations to estimate exposure are performed using a Monte Carlo approach—taking multiple repeated samples from the input files to generate an output distribution representative of any 1-day exposure for food, for the population of concern. The inputs for consumption are treated as fixed values. That is, as the iterative sampling is performed, reported consumption by an individual does not vary—it is what the individual reported consuming for that day of the survey. As a result, all diets in DEEM™ are “real”. That is, the diets represent actual reported consumption for a specific person. There are no unrealistic combinations or combinations that would not normally occur (such as mashed bananas and caviar!!). The residue that may be on any item consumed

that day is drawn from a distribution.¹ As shown in the following example, the residue values are randomly selected from all of the possible values in the residue distribution file for that food form.

Example Calculation

To make the following example simple enough to illustrate, we are using only two of the foods consumed by Person #1, and the very small residue files that were created for this example. Combining the consumption information with the residue information for the first Monte Carlo sampling iteration for Person #1, who reported eating apples and carrots, we might have:

<u>Food Consumed</u>		<u>Residues on Apples</u>			
		3 ppm	4 ppm	0 ppm	0 ppm
	Apples: 40 grams X  a randomly selected residue value from the apple residue file	3 ppm	4 ppm	0 ppm	0 ppm
		3 ppm	6 ppm	0 ppm	0 ppm
		3 ppm	6 ppm	0 ppm	0 ppm
		3 ppm	7 ppm	0 ppm	
		4 ppm	10ppm	0 ppm	
		4 ppm	0 ppm	0 ppm	

In this iteration, DEEM™ randomly selects 0 ppm as the residue value from this residue file. Therefore, the exposure estimated from apples, on this iteration, is:

$$40 \text{ grams} \times 0 \text{ ppm} = 0 \text{ mg}$$

¹DEEM™ also permits users to use a single value for a residue. This is what is termed a “deterministic assessment” in OPP. Since that single value which is entered into the file is generally at a tolerance or some “realistic high end” level, this is a very conservative (health protective) value. It is not generally used for individual chemical risk assessments and was not used for the preliminary OP cumulative risk assessment.

		<u>Residues on Carrots</u> <u>(cooked)</u>				
Carrots (cooked): 25 grams	X	{	a randomly selected residue value from the carrot (cooked) residue file	1 ppm	4 ppm	0 ppm
				1 ppm	5 ppm	0 ppm
				1 ppm	6 ppm	0 ppm
				2 ppm	0 ppm	0 ppm
				2 ppm	0 ppm	0 ppm
				2 ppm	0 ppm	0 ppm
				4 ppm	0 ppm	

In this iteration, DEEM™ randomly selects 2 ppm as the residue value from this residue file. Therefore, the exposure estimated from carrots, on this iteration, is:

$$25 \text{ grams} \times 2 \text{ ppm} = 0.05 \text{ mg}$$

To obtain person #1's total exposure estimate for this iteration (on a mg of pesticide per kg of body weight basis), for this day, based on this random sampling of residues:

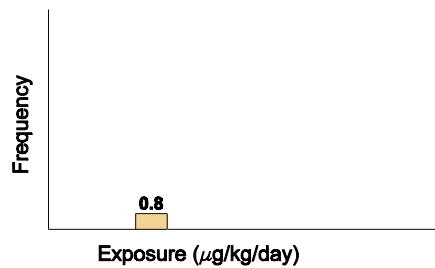
- ❖ Add together all of the exposures from all of the food forms consumed that day:

$$0 \text{ mg} + 0.05 \text{ mg} = 0.05 \text{ mg}$$

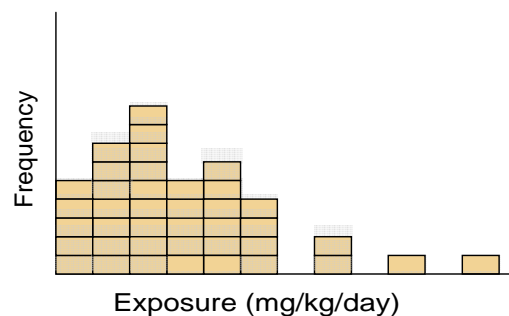
- ❖ Divide by Person #1's (self-reported) body weight (62 kg as reported in the CSFII) to get exposure in mg/kg (of body weight)/day:

$$0.05 \text{ mg}/62 \text{ kg} = 0.806 \mu\text{g}/\text{kg}/\text{day} = 0.000806 \text{ mg}/\text{kg}/\text{day}$$

- ❖ Place this exposure number (0.806 $\mu\text{g}/\text{kg}/\text{day}$) on a graph as illustrated below.

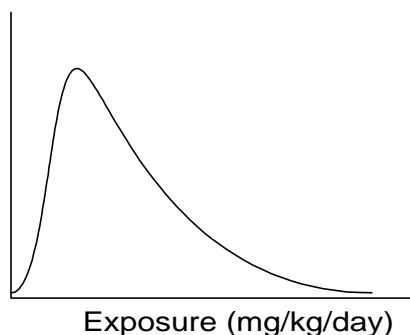


To begin to fill in the rest of the exposure distribution, these calculations are repeated approximately 1000 times for person #1's day one diet. Each time the calculation is repeated, the diet (that is the food forms and the amount of the food forms) of this individual remains the same while the residues are randomly selected from the residue distribution for each food form. Each of these "iterations" is a representation of "what might-have-been", that is, what pesticide residues that person might have been exposed to on that day. This process fills in the exposure distribution with approximately 1000 additional points. Taken together, these "might-have-beens" represent a collection of potential exposure events that portray the universe of exposures for this individual on this day. The process is then repeated another approximately 1000 times for Person #1 using the diet he reported on the second day of the survey, to generate another approximately 1000 points. These individual estimates continue to accumulate on the frequency histogram (i.e., the graph of the frequency distribution) and "build up" an exposure distribution, as illustrated below.



To complete the analysis, the process is then repeated approximately 1000 times for Person #2 using the diet that person reported on the first day of the survey and the same universe of residue files. Each of the estimated daily exposures is divided by the person's reported body weight and added to the distribution of estimated one day exposures. The process is repeated for day 2 of the survey for Person #2. The process is repeated for each person in the survey for both days of daily food consumption they reported, creating approximately 2000 potential exposure values per person.

When all of these exposure calculations are done, the graph will contain enough estimated values to approximate the total distribution of all one-day exposures for the population of concern. Sufficient iterations are conducted to ensure that the final estimates are "stable", that is, conducting additional iterations will have no effect on the resulting exposure distribution. Experience has shown that approximately 1000 iterations for each person-day are generally sufficient. The end result is a distribution of exposures for the U.S. population that represents the range and frequency of daily exposures that might be expected on any day, as illustrated below.

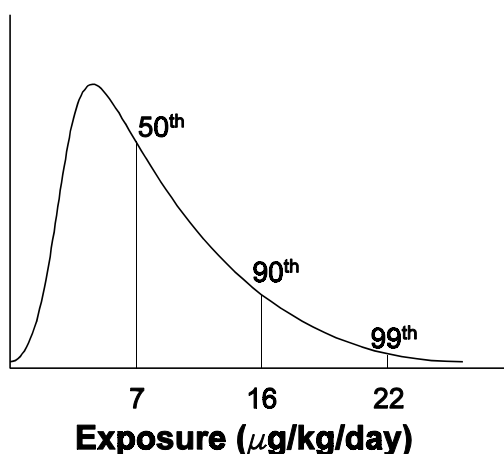


To obtain the relevant distributions for various sub-populations of concern, e.g., females 13 years and older, only the individuals who are members of that sub-population, e.g., females at least 13 years old, are considered.

Estimating Percentiles of Exposures/Calculating MOEs and Percent RfD or aPAD

Estimating Percentiles of Exposure

The above exposure distribution is used to obtain the exposure level(s) used in the risk assessments. To estimate percentiles, the distribution can be divided into 100 parts in such a way that each part represents 1% of the “person days” in the population (this is termed a percentile). Any desired percentile of exposure can then be determined from the distribution, as illustrated below.



For example, reading off the above exposure distribution:

- ❖ The 50th percentile is that exposure level where 50% of the exposures are less, and 50% are greater than that level. In this case, 50% of the population of concern would be expected to be exposed to less than or equal to 7 µg/kg/day on any given day and 50% would be expected to be exposed to greater than 7 µg/kg/day.
- ❖ At the 90th percentile of exposure (in this case 16 µg/kg/day), 90% of the population would be expected to be exposed to less than or equal to 16 µg/kg/day, and 10% would be expected to be exposed to greater than 16 µg/kg/day on any given day.

- ❖ At the 99th percentile of exposure (in this case 22 mg/kg/day) 99% of the population is expected to be exposed at 22 $\mu\text{g}/\text{kg}/\text{day}$ or less while 1% of the population is expected to be exposed at a level greater than 22 $\mu\text{g}/\text{kg}/\text{day}$ on any given day.

In the risk assessment for one-day exposure the selected exposure percentile(s) as described above is compared to the toxicological endpoint (effect) of concern. This can be done in several ways including, for example, as Margins of Exposure (MOEs), as a percentage of the Reference Dose (%RfD), or as a percentage of the Population Adjusted Dose (%PAD). These are illustrated below.

Calculating Margins of Exposure (MOEs)

If a Margin of Exposure (MOE) is used, the risk is calculated as:

$$\text{MOE} = \frac{\text{Acute or One-day Endpoint (e.g., a NOAEL)}}{\text{Exposure (at selected percentile of exposure)}}$$

In this example, if the 99th percentile of exposure were selected as an exposure level to evaluate in the risk assessment, the exposure (at this percentile) would be 22 $\mu\text{g}/\text{kg}/\text{day}$. If the endpoint is a NOAEL of 7500 $\mu\text{g}/\text{kg}/\text{day}$, then the MOE is:

$$\text{MOE} = \frac{7500 \mu\text{g}/\text{kg}/\text{day}}{22 \mu\text{g}/\text{kg}/\text{day}} = 341$$

The MOE calculation does not contain any consideration of uncertainty factors. Rather, a “target” MOE is often specified. For example, if the only uncertainty/safety factors being considered were the traditional 10X for potential inter-species variation and the 10X for potential intra-species variation, then the “target” MOE would be 100 (10x10). In this case, the estimated MOE of 341 would exceed the target MOE of 100, and exposure would not be of concern. If the target MOE were 1000 (based, for example on reflection of an additional 10-fold FQPA safety factor) the estimated MOE of 341 would be less than the target MOE of 1000, and the estimated exposure might be of potential concern.

Calculating Percentages of the Reference Dose (%RfD) or Population Adjusted Dose (%PAD)

If the risk is expressed as a percentage of the acute Reference Dose (%aRfD) or acute Population Adjusted Dose (%aPAD), some or all of the uncertainty/safety factors are included in the estimated risk. In the case of the Reference Dose, all uncertainty factors, except the FQPA safety factor, are included. The Population Adjusted Dose includes all uncertainty factors as well as the FQPA safety factor.

If the %aRfD is used to express risk, first the aRfD is calculated as:

$$\text{aRfD} = \frac{\text{Endpoint (e.g., a NOAEL)}}{\text{Uncertainty Factors}}$$

If the uncertainty factor = 100, then in our example:

$$\text{aRfD} = \frac{7500 \mu\text{g/kg/day}}{100} = 75 \mu\text{g/kg/day}$$

To express the risk as a percentage of the aRfD, the following calculation is used:

$$\%aRfD = \frac{\text{Exposure (at selected percentile of exposure)}}{\text{aRfD}} \times 100$$

$$\%aRfD = \frac{22 \mu\text{g/kg/day}}{75 \mu\text{g/kg/day}} \times 100 = 29\%$$

Since the result is less than 100% of the acute reference dose, the risk estimate does not exceed the level of concern in this case.

The %RfD calculation does not contain any consideration of the FQPA safety factor. If the FQPA safety factor is incorporated into the risk estimate, then the aRfD is converted to an acute Population Adjusted

Dose, using the following calculation:

$$\text{aPAD} = \frac{\text{aRfD}}{\text{FQPA Safety Factor}}$$

If the FQPA Safety Factor were retained at 10X then, in our example,

$$\text{aPAD} = \frac{75 \mu\text{g/kg/day}}{10} = 7.5 \mu\text{g/kg/day}$$

The percent of the aPAD is then calculated in the same way as the percent of the aRfD:

$$\% \text{aPAD} = \frac{\text{Exposure (at selected percentile of exposure)}}{\text{aPAD}} \times 100$$

In our example the result would be,

$$\% \text{aPAD} = \frac{22 \mu\text{g/kg/day}}{7.5 \mu\text{g/kg/day}} \times 100 = 293\%$$

Since the result is greater than 100% of the acute reference dose, the risk estimate exceeds the level of concern in this case.

II. Food & Water; One Chemical; One Day

The Importance of Using a Probabilistic Model for the Water Assessment

As discussed in the accompanying paper, in order to conduct a meaningful cumulative risk assessment it is necessary to use a distribution of (preferably daily) residue values for the water assessment. This is especially true for chemicals, such as OPs, for which the potential for concurrent or overlapping exposure must be evaluated. A probabilistic assessment which includes estimates of daily concentrations in water allows one to examine the temporal aspects of water exposure including co-occurrence in a realistic way.

The Spatial and Temporal Component of the Water Assessment

As noted in the discussion of food alone, foods are assumed to be “national” commodities because both agricultural commodities and processed foods are widely distributed. As the result of this assumption, where one lives is not important in the food only analysis. It is also assumed that the two days of diet reported in the CSFII are representative of a person’s diet on any day. Therefore, the day of the year is, in most DEEM™ analyses, not considered².

Water, on the other hand, cannot be considered a “national” commodity when performing a probabilistic assessment. The water one drinks is dependent on where one lives. While the bananas one consumes can originate from Honduras on one day and the Philippines on another, the source of the water one consumes will likely be the same each day. Thus, there is no “random allocation” of water as there is (to a great degree) with food.

Similarly, the amount of pesticide residues that may be in the water depends, among other things, on when pesticides are applied near the water source (especially for surface water sources) and, therefore, on the time of the year. For example, in most areas it is more likely that a residue peak will be present in May than in December. The probabilistic analysis of pesticide residues in water must account for these spatial and temporal components.

OPP addressed the spatial component of the analysis in the OP cumulative assessment by dividing the country into 12 regions and assessing water exposure separately for a specific location(s) in each region. Each of these regions reflects gross general differences in crops, farms, site and environmental factors, and pesticide use practices. As a result, instead of a single output distribution that represents everyone in a sub-population of concern there are multiple separate geographically-based distributions for each sub-population of concern. Each separate distribution represents exposures in one of the 12 regions of the country (with 1 region having 2 separate locations assessed).

To account for the temporal component of the water analysis, Calendex™ can use several different analysis types. Two of these types will be discussed in this document—“single day (specific)” which provides a distribution of daily exposures for any specific day the user selects, for example, February 3rd; and

²It is possible to perform a DEEM™/Calendex™ analysis which does consider the time of year of the reported consumption. This type of analysis is not currently done by the Agency. That is, reported consumption is assumed not to have a seasonal or other time component.

“multiple/week (sliding by day)” which provides distributions of daily exposures averaged over the combined number of days the user has selected.

Currently the number of days in the multiple/week option must be in multiples of 7 days up to one month, i.e., 7 days, 14 days, 21 days, or 28 days. For example, if a seven day (1 week) exposure averaging scenario is selected, Calendex™ sets up a scenario for seven sequential days, adds the exposures for each of the seven days together, and divides that exposure by 7 to get the average exposure for that seven days. In addition, this document will explain how these two different types of analyses can be used to produce distributions across the year, in the one case distributions based on daily exposures and in the other case distributions of seven day exposures.

Inputs

As in the case of food, there are two major inputs into the water exposure assessment—files on the amount of water consumed by each individual and files on the residues estimated to be in that water. The approach used to estimate daily pesticide concentrations in water predicts pesticide concentrations based on application timing, rate, and recorded weather data for that particular site. Although it is beyond current capabilities of the software, the water assessment in the future may use additional information on sources of drinking water consumed [e.g., bottled water vs. tap water] as well as information on the specific source of that water [e.g., a specific reservoir], but use of this level of detail was not included in the preliminary OP cumulative risk assessment.

Consumption Data

- ❖ The consumption data used for food, USDA’s CSFII, also includes each individual’s reported water consumption for each of the two days of the survey. This includes the amount of water the individual reported drinking or using for food preparation.
- ❖ Because of the limited sample size in the CSFII, rather than assigning people to the actual region where they live (which would result in very small samples for each individual region-- especially for different sub-populations in each region) all of the records in the CSFII are used in the calculations for each region. This is consistent with the “national” approach used for food exposures.
- ❖ Several methods could be used to account for different sources of drinking water. These include:
 - ▶ Estimating residues using the source of drinking water likely to have the highest residues (i.e., surface water for the OPs)

and assuming that the assessment covers (i.e., is protective of) all sources.

- ▶ Determining the proportion of people in each region who obtain their water from groundwater and the proportion who obtain their water from surface water. The sampling done to produce the exposure distribution would then reflect those proportions. For example, if 10% of the people in a region get their water from groundwater and 90% from surface water, then for 10% of the people, the model would go to the groundwater distributions to obtain the estimated residue value and for the remaining 90% of the people the model would go to the surface water distributions.

In the preliminary OP cumulative risk assessment estimated ground water concentrations were not included quantitatively in the risk estimates. However, in areas of the United States that receive their drinking water from ground water, monitoring data from vulnerable ground water sources were examined. In each region, it was determined that the surface water estimates would be protective of groundwater, i.e., the surface water estimates would be expected to be higher than any groundwater estimates. Therefore, the surface water estimates were considered to cover ground water.

Residue Data

- ❖ The preliminary OP cumulative assessment used available monitoring data to assess the vulnerability of groundwater to organophosphates, assist in choosing scenarios for modeling surface water, examining co-occurrence of pesticides, and evaluating modeling results at every level of the assessment process.
- ❖ The distribution of daily residue concentrations in surface water was estimated using the output of PRZM/EXAMS-IR modeling, which was based on typical use rates and typical application frequencies specific to the region of interest.
- ❖ This model uses approximately 36 years of actual reported weather data to model daily exposures for approximately 36 years at a particular site. (Some sites have less than 36 complete years of weather data available.)³

³The DEEM™/Calendex™ software can use any number of years, but the years must be complete (i.e., consist of 365 days of estimated water concentrations).

- ❖ The following example will illustrate the use of the PRZM/EXAMS-IR output to estimate daily residues.

As noted above, PRZM/EXAMS-IR was chosen for use in the OP cumulative assessment because it can evaluate daily concentrations of pesticides in water. The ability to obtain daily concentrations for use in a probabilistic assessment is critical to addressing the spatial and temporal components of the cumulative assessment in a realistic manner. The use of typical use rates and typical application frequencies in the assessment allows the focus of the OP cumulative assessment (unlike the individual chemical OP assessments) to be on the issue of likely co-occurrence of multiple OP pesticides.

As in the case of the individual OP chemical assessments, the available historical weather data (36 years of data for most sites) were used to develop the residue data files. These historical weather data provide the best available information on the variability in weather patterns at a specific location. These data are used in the model to estimate the resulting variability of pesticide residues in water. Because weather, specifically rainfall, is a very important factor in determining pesticide concentrations in water, these data are an important source of information that assist in estimating this variability. Using the PRZM/EXAMS-IR model, the historic weather data can be combined with current application practices and chemical-specific data for any given chemical to estimate daily pesticide concentrations for approximately 36 years. In the preliminary OP cumulative assessment, all of these daily values are used in a probabilistic assessment. In the individual assessments only one point from this distribution of approximately 36 years of data is used.

Preliminary Steps

- ❖ Country divided into relevant regions.
- ❖ PRZM/EXAM-IR is run for each scenario (defined as OP use on a single crop) in each region. The output of this process is a concentration value for each day of each of the approximately 36 years for which PRZM/EXAMS-IR has weather data. The resulting residue data files for a given region might look like the ones illustrated below. The variation that is illustrated from year to year in these files is the result of the variations in the weather data over the 36 years. All other inputs remain the same for each year in the analysis.

Residue File; Region1 Year One

Jan. 1	0.0035 ppm	Feb. 1	0.0030 ppm	etc., for each month of Year One, giving 365 residue values—one for each day
Jan. 2	0.0035 ppm	Feb. 2	0.0029 ppm	
Jan. 3	0.0034 ppm	Feb. 3	0.0029 ppm	
Jan. 4	0.0034 ppm	Feb. 4	0.0028 ppm	
.		.		
.		.		
Jan. 31	0.0030 ppm	Feb. 28	0.0028 ppm	

Residue File; Region 1 Year Two

Jan. 1	0.0012 ppm	Feb. 1	0.0010 ppm	etc., for each month of Year Two, giving 365 residue values—one for each day
Jan. 2	0.0012 ppm	Feb. 2	0.0009 ppm	
Jan. 3	0.0011 ppm	Feb. 3	0.0009 ppm	
Jan. 4	0.0011 ppm	Feb. 4	0.0009 ppm	
.		.		
.		.		
Jan. 31	0.0010 ppm	Feb. 31	0.0008 ppm	

etc., for each year that weather data are available, generally 36 years

This output is generated for each region (specifically, each location within a region) for 36 years, if weather data are available. Therefore, for most locations, there are 36 x 365 or 13,140 residue values available for use. This set of values provides a reasonable representation of the range of actual residue values to which individuals may be exposed.

Adjustments to the Residue Files

These residue data files contain the estimated concentrations of pesticides in a modeled reservoir in a particular region. These could be adjusted prior to running the assessment to account for water treatment, in cases where sufficient data are available on the effects of water treatment. Water treatment may affect the level of pesticides and/or pesticide degradation products in water that is actually consumed. For some pesticides, some types of treatment may remove residues or convert them to other forms. In addition different methods of treatment may have different effects. In most instances, lack of data and a high degree of variability in types of water treatment will preclude the Agency from making any definitive conclusions regarding treatment effects. In the case of the OPs available information was not sufficient to make quantitative adjustments to the cumulative exposure estimates.

Exposure Calculations

Putting the water consumption and water residue information together to estimate exposure is done using the same relationship as described for food:

$$\text{Exposure} = \text{Consumption} \times \text{Residue}$$

The calculations to estimate exposure are performed using a Monte Carlo approach. The inputs for water consumption are treated as fixed values. That is, as the iterative sampling is performed they do not vary--they are the amount of water the individual actually reported drinking and using for food preparation for that day of the survey. On the other hand, the pesticide residue estimated to be in the water consumed on that day will be drawn from a distribution. The residue values are randomly selected, for a given calendar date, from the approximately 36 years of available data, as illustrated in the following example.

Example Calculation

The following calculation illustrates the “single day (specific)” exposure calculations of DEEM™/Calendex™. This is the most basic method of DEEM™/Calendex™ exposure estimation. Using this type of analysis, exposure estimates are made for a single (*specified*) day, for example February 3rd. These daily estimates are the building blocks of other types of estimates and are illustrated in depth here to provide the basis for understanding an assessment for any time frame. It is not meant to represent a determination that single day exposure estimates are appropriate for the cumulative assessment. The method for developing an exposure distribution across the year (i.e., on each day of the year), based on a sequential series of single day exposures will be explained at the end

of this discussion. Calculations for *multiple* days (i.e., estimates based on average exposures over a series of days) will be explained in Section IV. “Multiple Days.”

Using DEEM™/Calendex’s™ “single day (specific)” method of exposure analysis, the user first selects the *specific day of interest*. The output from Calendex™ will be a distribution of potential exposures on that specific day (e.g., February 3).

Calendex™ first selects Person #1 in the CSFII and randomly assigns one of the two days of available diets reported by that individual in the CSFII. Using that diet together with randomly selected food residues from PDP, Calendex™ calculates Person #1's exposure through food as described earlier. To estimate exposure through water, Calendex™ randomly selects a year from the available approximately 36 years of output from PRZM/EXAMS-IR for that region and then selects the water concentration associated with the user-specified day (e.g., February 3). Person #1's CSFII-reported water consumption is multiplied by the selected water concentration to calculate exposure through water on that day.

Using the water residue values illustrated above, suppose that Year Two is randomly selected by DEEM™/Calendex™ for its first iteration for Person #1, and Person #1 reported in the CSFII consuming 2.5 liters of water for the diet selected. The following example presents the calculation which would be performed by DEEM™/Calendex™.

Daily Residue Values for ~36 Years for Region #1

Residue File; Region1 Year One

Jan. 1	0.0035 ppm	Feb. 1	0.0030 ppm	etc., for each month of Year One, giving 365 residue values—one for each day
Jan. 2	0.0035 ppm	Feb. 2	0.0029 ppm	
Jan. 3	0.0034 ppm	Feb. 3	0.0029 ppm	
Jan. 4	0.0034 ppm	Feb. 4	0.0028 ppm	
.	.	.	.	

Water
Consumed
2.5 liters X



The residue value for Feb. 3rd from a randomly chosen year, in this case Year Two

Jan. 31	0.0030 ppm	Feb. 28	0.0028 ppm
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Residue File; Region 1 Year Two

Jan. 1	0.0012 ppm	Feb. 1	0.0010 ppm	etc., for each month of Year Two, giving 365 residue values—one for each day
Jan. 2	0.0012 ppm	Feb. 2	0.0009 ppm	
Jan. 3	0.0011 ppm	Feb. 3	0.0009 ppm	
Jan. 4	0.0011 ppm	Feb. 4	0.0009 ppm	
.	.	.	.	

Jan. 31	0.0010 ppm	Feb. 31	0.0008 ppm
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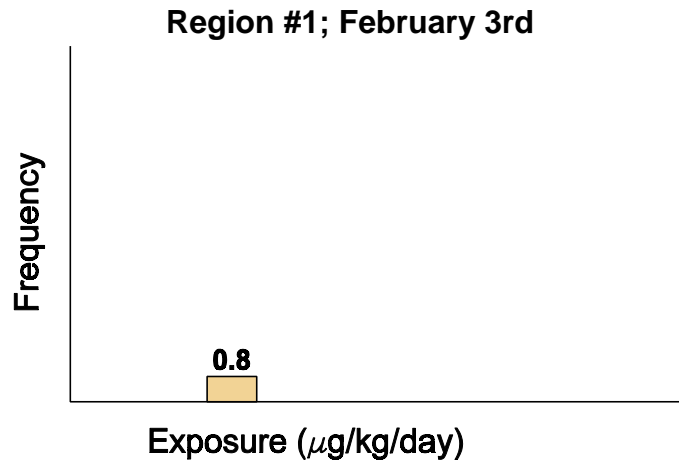
etc., for each of the years that weather data are available, generally 36 years

Calendex™ selects the water concentration associated with February 3rd (the user-selected day) of Year Two (here 0.0009 ppm). Therefore, the exposure from water on that day is:

$$2.5 \text{ liters X } 0.0009 \text{ ppm} = 0.0023 \text{ mg}$$

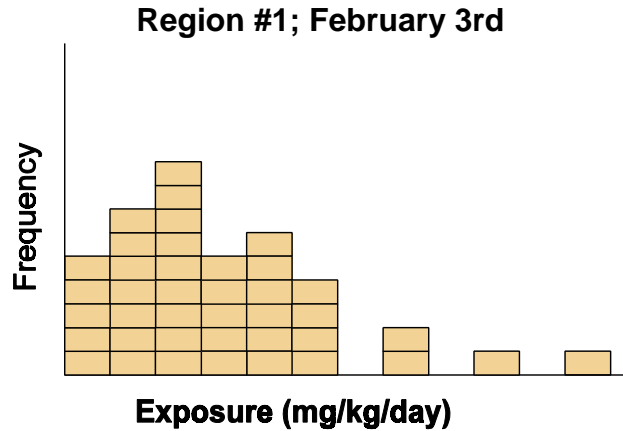
If person #1's estimated food exposure is 0.05 mg, this is added to the Feb. 3rd Year Two water exposure (0.0023 mg) to obtain the food + water exposure estimate, 0.0523 mg, for the first iteration of the assessment.

This is divided by Person #1's body weight (62 kg) to get exposure in mg/kg (of body weight)/day ($0.0523 \text{ mg}/62 \text{ kg} \approx 0.8 \text{ } \mu\text{g}/\text{kg}/\text{day}$). This one exposure number, $0.8 \text{ } \mu\text{g}/\text{kg}/\text{day}$, is placed on a graph as illustrated below.

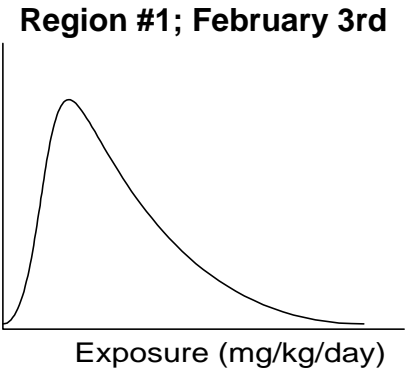


This graph, unlike the graph for food alone, is specific to a location because it uses modeled water concentrations that are based on factors specific to that location (e.g., pesticide use, soil type, weather data).

This process is then repeated multiple times for Person #1, first randomly selecting another year from the approximately 36 years of available water data, then randomly selecting one of Person #1's two recorded diets, next estimating pesticide exposure from that diet using randomly selected PDP residue values, and finally adding the estimated water exposure for February 3rd of the randomly selected year to the food exposure. These iterations fill in the exposure distribution with additional estimates for Person #1. As in the case of food alone, enough calculations are performed to achieve stability such that additional estimates do not change the resulting distribution of exposures. At the end of 40 such iterations, the distribution might be represented as shown below:



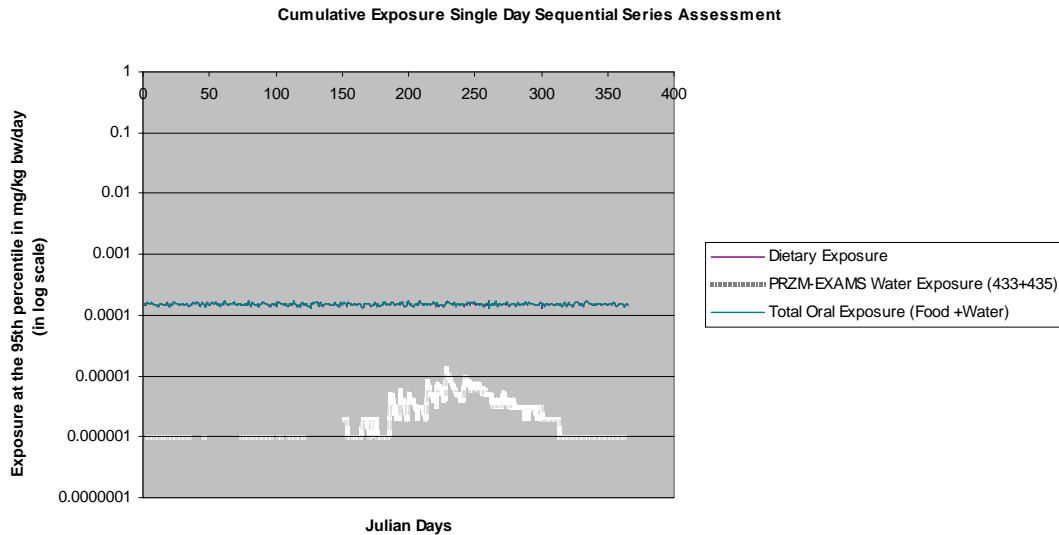
The process is then repeated for Person #2 for Region #1, first calculating this person's food exposure by randomly selecting one of the two reported diets and randomly assigning a residue value from PDP for each food included, then using the water consumption reported in the CSFII and a water concentration from February 3rd of a randomly selected year to estimate the water exposure. Each of Person #2's estimated daily exposures is divided by his reported body weight and the frequency distribution continues to be "built up". The process is repeated for each person in the CSFII who has two days of reported diets. The end result is a distribution of exposures for the region that represents the range of daily food and water exposures that might be expected on the user-selected day (here, February 3), as illustrated below.



To obtain the relevant distributions for various sub-populations of concern, e.g., females 13 years and older, only the persons who are members of that sub-population, e.g., females at least 13 years old, are included in that distribution.

As discussed above, in the case of food alone the Agency assumes the exposure estimates for all days can be combined in a single distribution that represents exposure on any day. Again, this is because it is assumed that exposure to food residues is not dependent on time of year or place of purchase of that food due to the wide distribution of both agricultural commodities and processed food. In addition diets are sampled so that they represent consumption throughout the year. This assures that the diets used are representative of the whole year. The exposure estimates for food alone are, therefore, presented as a single exposure estimate (for each percentile of exposure being considered).

In the case of water exposure, as discussed above, the expectation is different—exposure is assumed to depend directly on the day or time of the year. Exposures are expected to be different depending on the day, and exposure on sequential days is expected to be related. Thus, exposures are expected to show a pattern that is not random but directly reflects pesticide usage and weather that is particular to specific times of the year. As a result, the exposure estimates for water are not presented as a single number but as a time series throughout the year. An example of an output from this kind of analysis is shown in the following graph.



This time series is developed by calculating, for each of the 365 days of the year (as was done for February 3rd above), combined food and water exposure. For each calendar day, that day's distribution of exposures is used to obtain the exposure estimate presented in the time series (as explained in the accompanying document in Section V.C., "Interpretation of Model Outputs"). As in the case of food alone, any desired percentile of exposure can be obtained from the daily distribution. In the time series shown above, exposure at the 95th percentile has been taken from the daily distributions. However, any desired percentile of exposure can be obtained from the daily distributions and a time series for that percentile developed.

Specific days or weeks of the year in which concentrations in drinking water increased (during the spring run-off, for example) would appear as temporary "spikes" in any time series that is plotted. Such "spikes" might indicate to the risk manager that concentrations in water were contributing substantially to total (food + water) exposures and, if of concern, would provide additional information to the risk manager regarding possible mitigation actions.

As will be discussed below in Section IV. "Multiple Days" the building blocks of single day exposure estimates can be combined over the number of days specified by the user by adding single sequential daily exposures for an individual and dividing by the number of days to get the average exposure for that individual for those days. In that case, the resulting output distribution is a distribution of average exposures over a specified time frame, e.g. January 1st through January 7th. Single days

have been described here for simplicity, as well as because they are the building blocks for exposure assessments for longer periods of time.

III. Food & Water; Multiple Chemicals; One Day

In the case of multiple chemicals there are two major issues to address that do not arise in the case of single chemicals:

- ❖ how to compare and combine the toxicity of the multiple chemical residues
- ❖ how to assess the likelihood that multiple chemical residues are present at the same time

Comparing Toxicities of Multiple Chemical Residues

The method the Agency is using to combine residues from multiple chemicals adjusts all of the detected residues for each chemical, by their relative potency factor (RPF), as discussed in Section IV., “Endpoint Selection” in the accompanying paper. The RPFs reflect the toxicity of each chemical relative to an “index” chemical. Each residue value in the exposure assessment is adjusted by multiplying the residue by that chemical’s RPF. Once the RPFs have been developed, this is a simple mathematical adjustment to the residue files. The total (cumulative) exposure estimate is then presented as exposure to equivalent residues of the index chemical.

Assessing the Likelihood of Co-occurrence of Multiple Chemical Residues

Food

In the case of the food assessment for the OPs, the available PDP monitoring data which analyzes for multiple OPs provide a representative picture of the co-occurrence of the OPs on food.

Water

Determining when different chemical residues are likely to co-occur in drinking water sources, and when they are not is more difficult. The

Agency has examined the available monitoring data to determine the potential for co-occurrence of pesticides in water. The data confirm that co-occurrence does occur. The available monitoring data are discussed in detail in the accompanying paper. However, in estimating daily residue concentrations in water the Agency has used an in-depth analysis of pesticide usage, land usage, and potential of the location for runoff to get a more complete picture of possible co-occurrence. A discussion of the location selection process, usage data that were utilized, as well as example calculations of the cumulative adjustment factors for cropped area and OP crop use are presented in the accompanying paper.

The following steps highlight the assessment process used for each region:

- ❖ Use monitoring data to assist in identifying vulnerable surface water sources and to help assess likelihood of co-occurrence of multiple chemicals. In areas where groundwater is important analyze ground water monitoring information for the location.
- ❖ Determine which areas may be treated with OPs.
- ❖ Compile pesticide use data for each of these areas. Pesticide use surveys (such as those collected by NASS and the National Center for Food and Agricultural Policy) formed the basis of these data for most regions; the California Department of Pesticide Regulation, Pesticide Use Reporting Data was used for California. Where available, localized data sources were also used (for example, pesticide use in the Willamette Valley of Oregon was supplemented by data collected by Oregon State University).
- ❖ Determine high use areas within the region based on pesticide use and crops grown in the respective areas. These are the areas from which modeling sites were chosen. Available land use data (e.g., NLCD, USDA AgCensus) were used to indicate which crops are present in a particular high use area.
- ❖ Calculate Cumulative Adjustment Factors for the high use areas of interest.
- ❖ For each area of interest, run PRZM/EXAMS-IR model for all major OP-Site combinations, using chemical-specific data, typical usage patterns (application rates, application

methods, timing, etc.), meteorological data, and other surface water vulnerability factors relating specifically to that area.

- ❖ Scale the PRZM/EXAMS-IR output for each OP using the Cumulative Adjustment Factors calculated as:

PRZM/EXAMS-IR Output

$$\begin{aligned} & X (\text{Acres Treated}_{\text{OP/crop}} / \text{Acres Planted}_{\text{All OP Crops}}) \\ & X (\text{Acres Planted}_{\text{All OP Crops}} / \text{Total Acres}_{\text{In watershed}}) \end{aligned}$$

- ❖ Evaluate estimates using available monitoring data.

The PRZM/EXAMS-IR output provides the temporal information on the daily pattern of pesticide residues based on weather data and the timing of pesticide applications used in the model. This provides the basis for estimating co-occurrence. The model *initially* produces a calculation based on the whole area of the watershed being planted to OP treated crops and all of the area being treated. The scaling factor discussed above adjusts the output to reflect the best available estimates of the portion of the watershed actually planted to crops on which OPs are used ($\text{Acres Planted}_{\text{All OP Crops}} / \text{Total Acres}_{\text{In watershed}}$) and the proportion of acres treated for the particular OP crop combination being estimated, relative to all OP crops ($\text{Acres Treated}_{\text{OP/crop}} / \text{Acres Planted}_{\text{All OP Crops}}$). These adjustments allow a more realistic estimate of co-occurrence.

IV. Multiple Days

Calendex™ can estimate exposure on a single day, short-term, intermediate-term, or chronic basis. The exposure assessment illustrated above was the Single Day (specific) analysis, which is summarized below:

- ❖ Single Day (specific). In the single day (specific) analysis, for each iteration, exposure is calculated for a specific day specified by the user (e.g. February 3rd). The output provides a distribution of exposures for that specific day of the year. As illustrated above, these single day calculations can be viewed together to develop a sense of the patterns of exposures for the entire year. As discussed in the accompanying paper, using this mode of analysis and viewing the output over a year raises issues concerning the appropriate interpretation of examining the elevated exposure of different individuals over multiple days.

Among the many other types of analysis that Calendex™ can perform are

multiple weekly analyses. The following multiple week analysis will be described in this Section.

- ❖ Multiple Weeks (Sliding by Day). Currently this analysis can only be performed for 7 day increments up to 4 weeks, i.e., for 7, 14, 21, or 28 sequential days. Exposure is calculated for each individual for the specified number of sequential days (i.e., 7, 14, 21, or 28) that is selected by the user. The output is a distribution of sequential daily exposures averaged over the number of sequential days specified by the user. The following example illustrates this process using 7 days as the user selected number of sequential days. As discussed in the accompanying paper, using this mode of analysis raises issues concerning how appropriate the available data are for conducting such a longitudinal (multiple consecutive day) analysis for an individual.

Example Calculation Using the Multiple Weeks (Sliding by Day) Option

The following steps illustrate how drinking water exposure would be aggregated with food exposure using 7 days as the exposure period of interest. Because of the time-series nature of water exposure (and the fact that water concentration on one day is correlated with the water concentration on the previous day) it is necessary that the 7 days be a series of sequential days in order to get a realistic estimate.

The analyst would select a time period of interest e.g, the entire year, as was illustrated for the single day assessment. The user would provide Calendex™ with this information and instruct it that a 7-day (sliding by day) series should be calculated. DEEM™/Calendex™ would then proceed through the following steps:

For each location:

1. Calculate exposure from food for January 1st for Person #1 by randomly selecting one of his two diets and randomly assigning a residue value from PDP for each food included; after multiplying each amount of food consumed by its selected residue value the total exposure for food for this individual is calculated by summing the exposure through each food.
2. Repeat Step 1 for Person #1 6 times to represent that individual's diet for the next 6 consecutive days (i.e., January 2, January 3, January 4, all the way through January 7) each time randomly

selecting one of his two diets and randomly assigning a residue value from PDP for each food included. This will result in a total of 7 different daily exposure values for food representing January 1 through January 7.

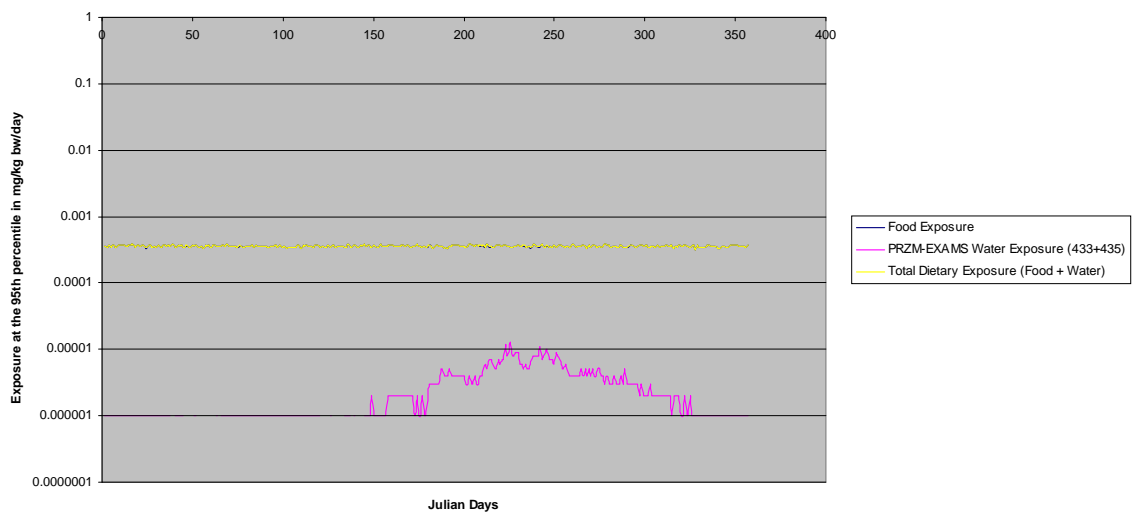
3. Calculate the 7-day *average* food exposure for this individual by summing the 7 individual daily exposure values and dividing by 7.
4. Randomly select a year from the range of values for which PRZM/EXAMS-IR estimated daily concentrations, for example, Year Twenty-three.
5. Select the PRZM/EXAMS-IR residue value associated with January 1st of Year Twenty-three.
6. Calculate the exposure from water for Person #1, for January 1st using this year Twenty-three water concentration value and one of the individual's two reported water consumption values.
7. Repeat Step 6 for the next 6 consecutive days (i.e., January 2, January 3, January 4, all the way through January 7) each time selecting the water concentration from this same originally selected year (Twenty-three). This will result in a total of 7 different consecutive daily exposure values for January 1 through January 7 in the randomly selected PRZM/EXAMS-IR year Twenty-three.
8. Calculate the 7-day *average* water exposure for this individual by summing the 7 individual daily exposure values and dividing by 7.
9. Calculate the total 7-day average (Food + Water) exposure for individual #1 for January 1st through 7th by adding the average food exposure for the 7-day period to the average water exposure for the 7-day period for this first iteration.
10. Repeat steps 1 through 9 for Person #1 for another randomly selected water year for the desired number of iterations, each time randomly selecting one of Person #1's two reported diets and randomly assigning a residue value from PDP for each food included, one of Person #1's two reported water consumptions, and a random year for water.
11. Repeat steps 1 through 10 for all of the individuals in the CSFII. The end result is a distribution of exposures for any January 1st through 7th that represents the range and frequency of exposures

that might be expected.

12. For the next (second) set of 7 days (January 2 through January 8) repeat steps 1 through 11, randomly selecting a new water year for each 7 day iteration.
13. Continue sliding the 7 day exposure period by 1 day and repeating steps 1 through 11 until the final sliding series eventually reaches December 31st.
14. Repeat the procedure for all locations.

The end result of this process is a series of 365, 7-day average, exposure estimates for the entire year. As described above in Section III, a time-series of these average 7-day exposures for the entire year can be constructed. In this case, the value for each day of the year represents an average value over 7 days, rather than a single day estimate. An example graph is displayed below.

Cumulative Exposure Seven Day Sequential Series Assessment at the 95th Percentile



OPP is continuing to pursue a series of analyses to evaluate alternative strategies for combining the data and selecting appropriate time frames to consider. This will be the subject of several questions presented to the SAP in February 2002.