Executive Summary

A. Introduction

In 1996 Congress enacted the Food Quality Protection Act (FQPA), which among other things, requires EPA to take into account when setting pesticide tolerances (maximum residue legally allowed on a food) "available evidence concerning the cumulative effects on infants and children of such residues and other substances that have a common mechanism of toxicity." Also, FQPA mandates that by 2006, EPA must review the safety of all existing tolerances that were in effect as of August 1996. The law requires EPA to place the highest priority for tolerance reassessment on pesticides that appear to pose the greatest risk, such as the organophosphorus (OP) pesticides.

To implement the cumulative provision of FQPA, EPA has been working to develop methodologies for conducting cumulative risk assessments and then conduct its first such risk assessment on the OP pesticides. This has been a challenging task given that historically, the potential health risks associated with exposure to pesticides has focused on *single pathways of exposure* (e.g., exposure from food, or water, or pesticide use in and around the home) for individual chemicals and not on the potential for individuals to be exposed to *multiple (common mechanism) pesticides by all pathways concurrently*, as is required under FQPA.

This scientific assessment of OP pesticide food safety contains good news for American consumers. After years of rigorous scientific work, it strongly supports our confidence that the United States has one of the safest food supplies in the world. Specifically, with this groundbreaking work, EPA has evaluated over 1,000 OP pesticide tolerances and virtually all of them are now consistent with the highest levels of safety. Please note that EPA is still evaluating the tolerances for a few of the OP pesticides.

This finding comes after years of scientific work, countless scientific and public meetings, and an existing regulatory process to ensure these pesticide tolerances meet the tough food safety standard in the Food Quality Protection Act. In the last several years, EPA has taken a variety of regulatory actions on the OP pesticides, ranging from lowering application rates to complete cancellations of specific uses. These actions have substantially reduced the risks and have contributed to the high level of safety found in the cumulative risk assessment.

On December 3, 2001 EPA issued for public comment its "Preliminary OP Cumulative Risk Assessment." That assessment was a preliminary review of the results of a new way of analyzing data regarding potential exposure to pesticides. The focus of the assessment was on the methods used to assess the risk. In contrast this revised risk assessment describes the potential risks of OP's by presenting a range of estimates that reflect the variability inherent in an assessment of this scope. Table 1 provides a side-by-side comparison of the major changes between the December 2001 and current documents. The changes were made due to comments submitted during the public comment period, suggestions from the FIFRA Scientific Advisory Panel (SAP), and issues that EPA was aware of at the time the preliminary cumulative risk assessment was issued but had not yet addressed. These major changes are discussed under "Hazard Assessment" and "Exposure Assessment," below.

With the release of this document the Agency has met its deadline obligation under a Consent Decree with the Natural Resources Defense Council to issue a revised risk assessment of the OP pesticides by August 3, 2002. As existing analyses are revised or new information is obtained, EPA will review this assessment and will make further changes as appropriate.

Not all of the changes result in quantitative impacts on the risk assessment. For example, in February 2002 the FIFRA SAP suggested that the Agency conduct more "sensitivity analyses" to assure the quality and robustness of the model being used (see text box). While these analyses provide valuable information on the reliability of the models, they do not change the quantifications of risk (e.g., MOEs). On the other hand, other changes do impact the risk quantification. During the public comment period food processing factors were submitted; EPA has updated its food exposure estimates using this information.

Sensitivity Analysis is the study of how the variation in the output of a model can be apportioned to different sources of variation–it aims to ascertain how the model depends upon the information fed into it, upon its structure, and upon the assumptions made to build it. Overall, sensitivity analysis is used to increase the confidence in the model and its predictions by providing an understanding of how the model response variables respond to changes in the inputs.
http://sensitivity-analysis.jrc.cec.eu.int/default.htm

It has become evident that addressing issues such as the FQPA Safety Factor and the threshold of concern are both dependent on the available data. The decisions made regarding these two issues involve risk management considerations and will be made on a case-by-case basis. EPA intends to use a systematic approach in making these decisions to reflect such factors as the quality of the available data and the characteristics of the modeling analysis.

Table ES-1. Major Differences Between the Preliminary OP Cumulative Risk Assessment and the Revised OP Cumulative Risk Assessment

	December 2001	June 2002
Toxicity		
Relative Potency Factors (RPF's)	Used best available data	Additional RPF's were calculated: chlorethoxyphos, phostebupirim, profenofos and omethoate (a metabolite of dimethoate)
FQPA Factor	Not addressed	FQPA Safety Factors were assigned based on available information; 1X for three OP's and one metabolite; 3X used for the others
Treatment of Animal Data	Used means and standard deviations	To see how the results would be affected, single animal data were used in a sensitivity analysis
Exposure		
Food: Processing Factors	Used best available data	Revised based on data provided during the public comment period
Consumption Data	Used the CSFII data "as is"	Conducted a sensitivity analysis to look for 'extreme' outliers
Residue Data	Did not use any over-tolerance residues	Included over-tolerance residue values
Impact of High-End Exposure	Not considered	Conducted an analysis to determine whether specific high-end consumption and/or residue values are significantly responsible for the exposure estimates at the higher percentiles of the exposure distribution
Duration of Exposure	One-day	One - and seven-day rolling average. Also, a sensitivity analysis was conducted using 14- and 21-day rolling averages
Populations Considered	The standard populations	Conducted a sensitivity analysis by looking at additional subpopulations
Drinking Water: Number of Regions*	13	7; EPA found that a number of the Regions could be combined due to similarities among geography, climate, and soil type
Sensitivity Analysis	Some performed	Extensive analyses conducted, as suggested by the SAP
Residential: Populations Considered	The standard populations	Conducted a sensitivity analysis by looking at additional subpopulations
Type of Distribution	Uniform	log normal, as recommended by the SAP
Number of Regions[1]	13	7; EPA found that a number of the Regions could be combined due to similarities among geography, climate, and soil type
Pet Uses	Not included	New data on tetrachlorvinphos
Risk		
Risk Quantification	Summary results; MOE's for single-day exposures at various percentiles of exposure	Identified pestide/crop combinations that have significant roles in the estimates. Risk presented as ranges of MOEs at various percentiles reflecting one- and seven-day exposures, and 14 and 21-day rolling averages

[1]A Note on "Regions." Because the United States is so climatologically and geographically diverse, EPA has divided the country into different risk assessment "Regions" so that this diversity could be factored in to the assessments.

B. Hazard Assessment

1. RPF's

The RPF's were revised and relative potency factors for four additional chemicals have been calculated (chlorethoxyphos, phostebupirim, profenofos, and a metabolite of dimethoate).

2. FQPA Safety Factor

In the December 2001 preliminary cumulative risk assessment, EPA discussed and characterized the potential multiple sources of exposure to children but did not address the FQPA Safety Factor. The decision regarding the Safety Factor is determined based on the available data for the specific chemicals in this assessment. The Revised OP Cumulative Risk Assessment provides an analysis on the sensitivity and susceptibility of infants and children to cholinesterase (ChE) inhibition (the common mechanism of toxicity) caused by OP pesticides.

In summary, based on available information, the FQPA Safety Factor is 1X for three OP's and one metabolite (dimethoate; omethoate, a metabolite of dimethoate; chlorpyrifos; and methamidophos) and 3X for the remaining OP's. A summary of the rationale is provided below; please note that these Safety Factors are appropriate for this risk assessment only.

- ❏ In making an FQPA Safety Factor decision, EPA considers both the potential for pre- and postnatal toxicity and the completeness of the toxicology and exposure databases (USEPA, 2002a). Looking at the exposure side of the equation–there is a high degree of confidence in the exposure data and methodologies used–EPA believes that it is not necessary to retain the default 10X FQPA Safety Factor based on the exposure database.

- ❏ The toxicity endpoints for this assessment were developed in consideration of a 10X uncertainty factor to account for interspecies variability and a 10X uncertainty factor to account for intraspecies variability. Because some OP pesticides show age-dependent sensitivity and there are missing comparative ChE inhibition data in young animals for many of the OP's, EPA chose an FQPA Safety Factor of 3X for most of the OP pesticides. There were a few whose data supported a 1X FQPA Safety Factor:

  – Age-dependent susceptibility data are available for seven of the OP's. The data for dimethoate, omethoate (a metabolite of dimethoate), chlorpyrifos, and methamidophos support an FQPA Safety Factor of 1X.

On June 25 to 27, 2002 EPA is consulting with the FIFRA Scientific Advisory Panel on this sensitivity and susceptibility analysis for children. For more information see: http://www.epa.gov/fedrgstr/EPA-MEETINGS/2002/May/Day-31/.

For future cumulative risk assessments the FQPA Safety Factor may be retained, reduced, or removed, based on the available data which are specific to the chemicals examined.

C. Exposure Assessment

1. Regions

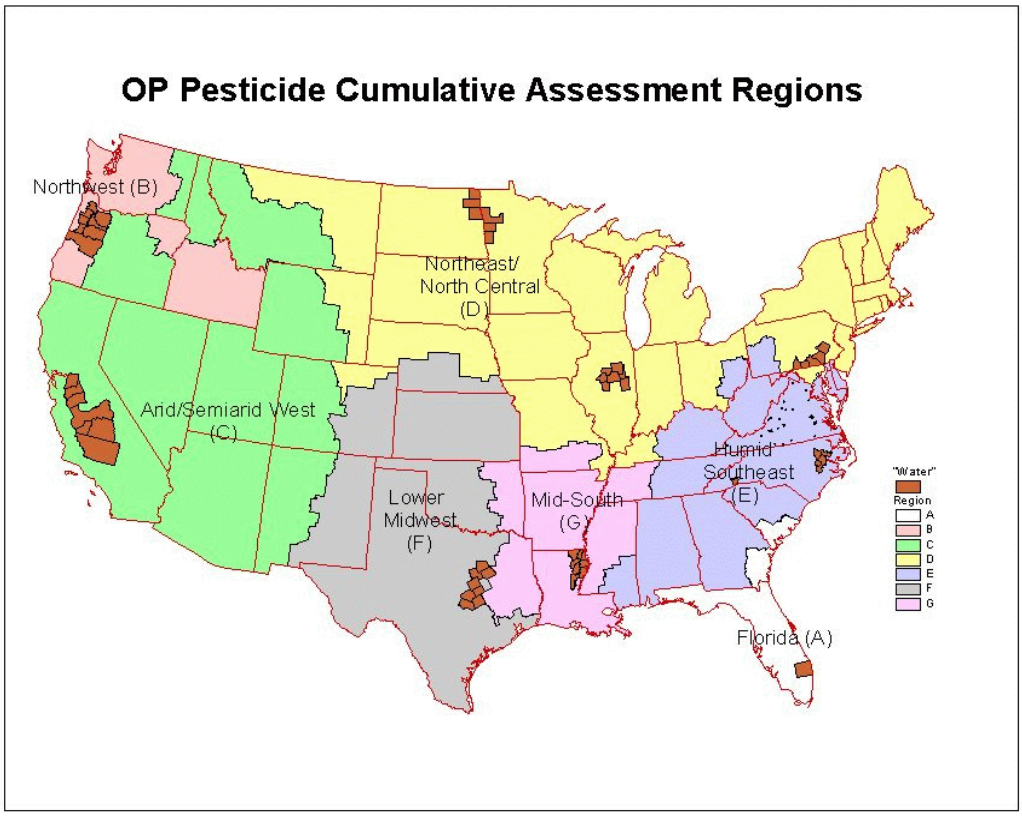
Because the United States is climatologically- and geographically-diverse, EPA divided the country into Regions so that it could account for factors such as weather and soil type (these affect the amounts and types of pesticides used). In the December 2001 analysis 13 Regions were used; the current analysis has seven. The reason for this reduction is that EPA realized that some of the Regions were not truly distinct so they were combined. Provided in Figure ES-1 is a map of the United States that shows the seven Regions.

As mentioned in the "Introduction" sensitivity analyses were conducted for a number of variables. The exposure data used for these analyses were from Region A. EPA chose Region A because it has the highest estimated exposure.

2. Food

The amount of pesticide to which an individual is exposed (i.e., exposure) is determined by combining the amount of pesticide that is in or on the food (i.e.,

ES-1. Regions Used for Exposure Assessment



YSHQ, BS(HED), 2002

residue levels) and the amount and type of foods that people eat (i.e., food consumption). In the Revised OP Cumulative Risk Assessment EPA conducted a number of sensitivity analyses on the data and models supporting the food risk assessment.

Consumption Data. EPA uses USDA's Continuing Survey of Food Intake by Individuals (CSFII) for its food consumption data. One of the criticisms that has been raised regarding the food consumption data is that it may include individuals who have "extreme" diets. EPA scientists, including a nutritionist, have conducted a sensitivity analysis on the food consumption database; no outliers were identified. Consumption data that appeared unusually high and were associated with high exposures in the cumulative risk assessment were fully investigated.

Although they did not identify any outliers, it is important that appropriate sensitivity analysis be conducted so that any outliers are evaluated. Please note that several individual OPs are still undergoing individual assessments and for these pesticides future analysis on food consumption will continue.

Residue Data. All of the residue data in this assessment came from USDA's Pesticide Data Program (PDP) and FDA's Center for Food Safety and Applied Nutrition (CFSAN) monitoring data. In the Revised OP Cumulative Risk Assessment EPA incorporated over-tolerance residue values from the PDP data.

Impact of High-End Exposure. The December 2001 document pointed out that:

> The data inputs and assumptions need to be verified, and the results at the tail end of the distribution at the higher percentiles of exposure for children's age groups need to be evaluated to ensure they reflect reasonable consumption patterns. Additionally, OPP is in the process of conducting sensitivity analyses that will permit a fuller characterization of the contributors or sources of potential risks associated with the food pathway.

The Revised OP Cumulative Risk Assessment includes an analysis of the upper tail of the exposure distribution to determine whether specific high-end consumption and/or residue values are significantly or mainly responsible for the exposure estimates at the higher percentiles of the exposure distribution. In addition, a range of percentiles of exposure as well as the percentiles at which the MOEs approach 100 (100 because the toxicity endpoints for this assessment were developed in consideration of a 10X uncertainty factor to account for interspecies variability and a 10X uncertainty factor to account for intraspecies variability) are presented in the body of the risk assessment. This information provides the basis for bounding and characterizing exposures.

Duration of Exposure. In the December 2001 risk assessment EPA used one-day as the duration over which an individual would be exposed to a pesticide residue in food. However, this analysis overestimates risk because the toxicity data and consumption reflect different time frames. For the current analysis EPA added a second exposure duration, that of the seven-day rolling average in an attempt to better match the time frames for the toxicity data with the consumption data which are not directly comparable. EPA also believes using these time intervals will bound the risk (i.e., the potential risk is best represented by a range of values for different exposure durations). In addition the Agency evaluated 14- and 21-day averages for one Region (Region A). EPA conducted these additional analyses to determine whether estimates of average daily exposure changed significantly over longer durations.

The chart provided below (Table ES-2) provides a discussion of how the one- and seven-day durations are affected by four key factors.

Table ES-2. How the One- and Seven-Day Durations Are Affected

Factor	Impact on Durations
The degree to which the exposure and toxicity time frames correspond to each other.	The use of a steady state hazard endpoint–based on toxicity studies that are 21-days or longer–tends to overstate the risk for the one-day analysis. Use of the steady state value is more appropriate with the 7-, 14-, and 21-day analyses.
The degree to which the Agency has captured the previous day's cholinesterase inhibition.	For the one-day analysis, the consideration of only a single day's exposure may underestimate risk, to the extent an individual's previous days' exposures continue to cause ChE inhibition. For the same reason, multiday exposures may also underestimate risk.
Day-to-day variation in individuals' diets.	Day-to-day variability in an individual's diet does not affect the one-day estimate. Limited data about such variability requires EPA to make assumptions that tend to underestimate the potential exposures for the seven-day analysis.
Possible correlation among residues on different days.	EPA's multiday analyses do not account for the possibility that a person may be more likely to encounter high residues in food because some portion of their consumption comes from the same source. This limitation means that multiday analyses may underestimate food exposure somewhat. This limitation does not affect the one-day analysis.
Interpretation of Model Outputs	The one-day analysis assumes that an individual is exposed to OP residues from the tail of the distribution every day. This assumptions overestimates risk. The seven-day analysis incorporates day-to-day variability in exposure and is more representative of anticipated exposures.

The Agency believes the timeframe considerations, as they relate to both hazard and exposure, to be among the most important for the OP cumulative assessment. This is not surprising since the essence of the cumulative assessment is to estimate likely co-occurrence in exposure to multiple chemicals and the likely combined effect of those exposures.

Populations Considered. Standard population subgroups that EPA considers in dietary risk assessment include: children one- to two-years-old; children three- to five; adults 20 to 49; and adults 50 and older. Upon SAP's recommendation, EPA looked at other subpopulations such as infants less than one year and teenagers. This was done to demonstrate that indeed children one- to two-years-old are the most highly exposed, due to their high consumption-to-body weight ratio.

3. Drinking Water

EPA evaluated the contribution to overall exposure resulting from OP pesticide residues in drinking water across different Regions and found that drinking water is not a significant source of exposure. EPA looked at the impacts that periods of high-volume runoff (e.g., during the spring and storm events) have on the level of pesticide residue estimated in drinking water. It was found that there are higher concentrations of pesticides in the drinking water during such periods. The analysis shows that, even considering such events, drinking water is not a significant contributor to overall risk.

4. Residential

Populations Considered. The population subgroups that EPA considers for residential exposure are the same as those considered for the food exposure. Similar to the food assessment, EPA conducted sensitivity analyses by looking at additional subgroups such as infants. This was done to see how including more population subgroups would change the risk estimates. The Agency is still working to evaluate individual residential uses (as part of the cumulative assessment) where additional risk mitigation will likely be necessary. In the next several weeks, EPA will continue the scientific and regulatory work to evaluate and address these potential risks.

Type of Distribution. EPA reassessed residential exposure using log-normal distributions of the available data (instead of a uniform distribution), wherever possible. This change was made because, according to the SAP, a log-normal distribution better represents the data set. Some of the resulting residential exposure estimates, and in turn risk, are lower than the December 2001 estimates.

Pet Uses. New data on exposure from the pet uses of tetrachlorvinphos have been used to quantitatively include tetrachlorvinphos in the residential assessment.

D. Risk Characterization

The risk characterization summarizes and integrates all of the information from the various components of the assessment. Risk characterization looks at the strengths and weaknesses of the data used, including any potential biases in input parameters and the direction of that bias, reliability and availability of the data, as well as the characteristics of the exposure models, and attempts to bound that uncertainty. The revised assessment discusses in great detail what data have been used; how the data have been used; and the strengths and weaknesses of the resulting analysis.

The risk estimates presented in this Revised OP Cumulative Risk Assessment are the culmination of several years of Agency analyses, outside input, and risk mitigation efforts on the part of the regulated community. Beginning in the summer of 1998 EPA started to seek public input on its individual OP risk assessments by issuing *Federal Register* notices asking for comment. In addition, EPA actively sought the advice of the regulated community, environmental groups, and others through two Federal advisory committees, the Tolerance Reassessment Advisory Committee (TRAC) and the EPA-USDA Committee to Advise on Reassessment and Transition (CARAT).

Throughout this period of public review and scrutiny, a good deal of risk reduction has been achieved through the risk mitigation measures taken on the individual OP's. In 1996 49 OP pesticides were registered for use in agriculture and residential settings. Today, 14 of those pesticides have been canceled completely and for another 28, considerable risk mitigation actions have been taken. For example:

- ❏ Methyl Parathion. Methyl parathion had been one of the most widely used OP's. In 1999 the registrants voluntarily canceled many methyl parathion uses that contribute most to the children's diet. These included: apples, peaches, pears, grapes, nectarines, cherries, and plums, carrots, succulent peas, succulent beans, and tomatoes.

- ❏ Ethyl Parathion. Before 2000, ethyl parathion had been one of the most highly restricted pesticides registered for use in the United States. A 2000 agreement canceled all remaining uses of the OP pesticide ethyl parathion, which included use on nine agricultural crops. Use of parathion on corn grown for seed was to stop immediately, with the use on other crops to be phased out over the next few years.

- ❏ Chlorpyrifos. Before the risk mitigation measures were taken, chlorpyrifos had been one of the most widely-used pesticides in and around the home. It is also one of the most widely used OP pesticides in agriculture. In 2000 the registrants agreed to cancel nearly all indoor and outdoor residential uses, as well as use on several food crops that contributed most to children's dietary exposure.

- Diazinon. Diazinon is one of the most widely used agricultural insecticides and until 2000, one of the most widely used insecticides for household lawn and garden pest control. In 2000 all indoor residential uses were terminated; outdoor residential uses will be phased-out over the next several years. Additionally, many agricultural uses of diazinon also are being canceled.

Without these measures, pesticide exposure through food and in and around the home would have been more significant. December's preliminary analysis and now the revised analysis reflect all these important risk mitigation measures.

1. Risk Quantification

This version of the cumulative risk assessment presents results showing a range of estimated risks depending on the exposure period considered (one-day or seven-day average) and the percentile of exposure. Ranges of estimated risk at various percentiles of exposure are also presented for 14- and 21-day averages for Region A. The selection of the range for the percentile of exposure must take into account the data from the particular group of chemicals in the assessment. For most portions of the ranges presented from the different exposure periods, the estimated Margins of Exposure (MOEs) do not represent levels of potential concern. After careful analysis, the Agency believes that the potential exposures are bounded by the estimates for the one- and seven-day exposure durations, and generally the margins of exposure in this assessment do not represent major concerns.

In considering the possible need for risk mitigation actions, EPA believes that it is important to consider the range of risk assessment values, which in turn take into account different exposure periods, for different age groups, living in different Regions, with risks shown at different percentiles of estimated exposures. It is also important to consider risk characterization, including the factors that may tend to overestimate or underestimate risk, and the identification of major sources contributing to potential exposure.

It appears that one of the major factors influencing the results at the highest portion of the range derives from the fact that, for a few individual OP's, risk assessments and mitigation actions have not been finalized. This is particularly true for DDVP and dimethoate. The Agency expects to complete these risk assessments and possible mitigation actions very soon.

Finally, it is important to remember that portions of this document are currently under review by the FIFRA SAP. For instance, EPA intends to present preliminary results of cumulative risk using two additional models–CARES and Lifeline™–to the SAP during the June 2002 meeting. EPA will evaluate SAP's comments, as well as other comments or data that it receives, and will modify this assessment, as appropriate. In addition, as existing analyses are revised or new information is obtained, EPA will review this assessment and will make further changes as appropriate.

E. Conclusion

This scientific assessment of OP pesticide food safety contains good news for American consumers. Regulatory actions taken over the last six years have considerably reduced the risks posed to Americans from OP residues that may be found in food, drinking water, and in and around the home. After years of rigorous scientific work, the Revised OP Cumulative Risk Assessment strongly supports our confidence that the United States has one of the safest food supplies in the world.

F. Road Map

The Revised OP Cumulative Risk Assessment is divided into three parts: (1) the actual risk assessment which draws on the regional risk assessments and the supporting toxicology analyses (I. Revised OP Cumulative Risk Assessment); (2) the seven regional risk assessments (II. Revised Regional Assessments); and (3) the detailed toxicology analyses such as the derivation of the RPF's and how the FQPA Safety Factors were determined (III/ Appendices).