Technical Executive Summary

EPA has completed the preliminary cumulative risk assessment for the organophosphorus pesticides (OPs). The assessment is a preliminary view of the results of a new way of analyzing data about potential exposure to pesticides. The Agency's methods result in well developed measurements of the probability of exposure to more than one organophosphorus pesticide. While OPP is interpreting the results of these analyses, it is too soon to draw firm conclusions about risks or consider risk management possibilities. The risk mitigation measures that have already been taken on individual members of this group of pesticides have led to significant reduction in potential risk, and EPA is continuing to address risks as they are identified for individual OPs. EPA continues to have confidence in the overall safety of our food supply and emphasizes the importance of eating a varied diet rich in fruits and vegetables. Organophosphorus residues in drinking water do not appear to contribute substantially to exposure. Although most indoor uses of organophosphorus pesticides have been eliminated through earlier risk reduction actions, a small number of remaining uses may be of concern.

By 2006, under Federal law, EPA must review the safety of all existing tolerances (maximum residue allowed on a food) 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 pesticides. Over the last several years, the Office of Pesticide Programs (OPP)has been conducting risk assessments for individual organophosphorus pesticides and taking regulatory action to reduce exposure to these pesticides. As part of the tolerance reassessment process under the Food Quality Protection Act (FQPA) of 1996, EPA must consider available information concerning the cumulative effects on human health resulting from exposure to multiple chemicals that have a common mechanism of toxicity. A cumulative risk assessment also incorporates exposure data from multiple pathways (i.e., food, drinking water, and residential/non-occupational exposure to pesticides in air, or on soil, grass, and indoor surfaces).

The cumulative assessment of risks posed by exposure to multiple chemicals by multiple pathways presents a formidable scientific challenge. To meet this challenge, OPP began developing new tools and methods for conducting cumulative risk assessments on pesticide chemicals shortly after the enactment of FQPA. OPP has relied on the FIFRA Scientific Advisory Panel (SAP) to peer review these methods and pilot analyses using actual data sets on organophosphorus pesticides to ensure that OPP is using appropriate methods and sound science. The SAP has recognized and reacted favorably to the ground-breaking nature of OPP's methods development. In addition to the SAP reviews, EPA has sought and considered public comments on these approaches.

There are many steps involved in quantitatively assessing the potential human risk associated with the organophosphorus (OP) pesticides. Several key steps include:

① selection of the pesticides, pesticide uses, routes, and pathways from the full group of OPs with exposure and hazard potential to include in the quantitative estimates of risk,

② determination of the relative toxic contribution of each OP, selection of an Index Chemical to use as the point of reference to standardize the toxic potencies of each OP, and establishment of a value to estimate potential risk for the group,

③ estimation of the risks associated with all pertinent pathways of exposure in a manner that is both realistic and reflective of variability due to differences in location, time and demographic characteristics of exposed groups,

④ identification of the significant contributors to risk, and

⑤ characterization of the confidence in the results and the uncertainties encountered in the assessment.

The complex series of evaluations involved hazard and dose-response analyses, assessments of food, drinking water, and residential/non-occupational exposures, and risk characterization. The approach to each of these components and their results is briefly explained below.

A cumulative risk assessment begins with the identification of a group of chemicals, called a common mechanism group, that induce a common toxic effect by a common mechanism of toxicity. Pesticides are determined to have a "common mechanism of toxicity" if they act the same way in the body--that is, the same toxic effect occurs in the same organ or tissue by essentially the same sequence of major biochemical events. Because organophosphorus pesticides have been assigned priority for tolerance reassessment, these pesticides were the first common mechanism group identified by OPP (see *"A Common Mechanism of Toxicity: The Organophosphate Pesticides"* in OPP's *Guidance For Identifying Pesticide Chemicals and Other Substances That Have A Common Mechanism of Toxicity* available at:

http://www.epa.gov/pesticides/trac/science

The inhibition of acetylcholinesterase is the common effect for the organophosphorus pesticides. Acetylcholinesterase is an enzyme that regulates a neurotransmitter, acetylcholine. If cholinesterase is inhibited by OP exposure, the nerve impulses remain active too long and overstimulate the nerves and muscles.

Once a common mechanism group is identified, it is important to determine what chemicals from that group should be included in the quantification of cumulative risk. In choosing OPs for the cumulative risk assessment, EPA considered risk mitigation decisions and exposure potential. There are 39 cholinesterase-inhibiting

organophosphorus pesticides registered by EPA. The eight pesticides excluded from the assessment are being phased out based on agreements with the registrants or have negligible, if any, exposures according to their individual risk assessments. The 31 pesticides considered in this analysis (listed in Table 1 at the end) were selected based on their detection in USDA's Pesticide Data Program (PDP), which collects monitoring data on pesticide residues in commonly eaten children foods such as fruits, vegetables, and milk, as well as their potential for human exposure through residential or non-occupational uses and/or drinking water.

EPA identified three exposure pathways: food, drinking water, and residential/non-occupational. Each of these pathways was initially evaluated separately, and, in doing this step of the analysis, EPA determined which of the OPs were appropriately included for a particular pathway. The cumulative assessment of potential exposure to OPs in food includes 22 OP pesticides that are currently registered in the U.S. or have import tolerances. Although17 OPs had registered uses in residential and public areas before the reassessment process began, the assessment of this exposure pathway considers only 10 OPs because many residential uses have been canceled as a result of risk mitigation efforts or are not expected to result in any significant exposure. The current assessment reflects the most up-to-date residential use picture for these chemicals. Twenty-four pesticides (as well as several toxic transformation products) were considered in the cumulative water exposure assessment.

EPA used the relative potency factor (RPF) method to determine the joint risk associated with exposure to these OPs. Briefly, the RPF approach uses an index chemical as the point of reference for comparing the toxicity of the OPs. Relative potency factors (i.e., the ratio of the toxic potency of a given chemical to that of the index chemical) are then used to convert exposures of all chemicals in the group into exposure equivalents of the index chemical. Because of its high quality dose response data for all routes of exposure, EPA selected methamidophos as the Index Chemical for standardizing the toxic potencies and calculating relative potency factors for each OP.

Toxic potencies for the OPs were determined using a common endpoint derived from the same laboratory animal species and sex for all three exposure routes of interest (i.e., oral, dermal, and inhalation). Brain cholinesterase inhibition from female rats was determined to be a common and appropriate endpoint for estimating the relative toxic potency of each OP. Brain cholinesterase inhibition is a direct measure of the mechanism of toxicity, and thus does not have the uncertainty associated with using blood measurements of cholinesterase inhibition, which serve as surrogates for cholinesterase inhibition in the peripheral nervous system. Furthermore, relative toxic potencies derived from brain data were generally similar to those derived from red blood cell data and showed less variability, and thus less uncertainty.

The determination of each OP's toxic potency was based on cholinesterase inhibition data from exposures of rats for 21 days or longer. Monitoring data show that people generally have had some level of OP exposure, making it unlikely that any individual would encounter exposure to OP pesticides without having a previous exposure from other sources. Therefore, EPA does not consider the use of toxic

endpoints based on single-day exposures to be reflective of the actual human exposure situation. Furthermore, the effects of OPs exposure can persist for several days to weeks depending on the magnitude of exposure, making the exposed individual potentially more vulnerable to subsequent exposures during that period. Finally, data collected after test animal exposures of 21 days or longer have very stable and reproducible levels of cholinesterase inhibition, making determination of relative toxic potencies among the OP pesticides more reliable.

An exponential dose-response model was used to determine relative toxic potencies of the OP pesticides for the oral cholinesterase data. The SAP reviewed this model and favorably received it as an appropriate approach. EPA refined the model fitting strategy based on the SAP recommendations. Because the dermal and inhalation data were not as robust and extensive, relative toxic potencies were evaluated based on comparative effect levels rather than dose response modeling. The points of departure (POD) for the index chemical, methamidophos, were derived using the exponential model for each route of exposure (i.e., oral, dermal, and inhalation). The POD is the point in the dose-response curve at which a change in response can be reliably said to be due to dosing with the chemical. EPA uses the POD value with exposure information to estimate potential risk to humans.

Three key pathways of exposure to OP pesticides–dietary pathways of food and drinking water, and the nondietary pathway from exposure in residential and other non-occupational settings–were included in this assessment. An important aspect of the exposure analyses is to develop exposure scenarios resulting from the uses for each OP. Factors EPA considered in this analysis included duration, frequency, and seasonality of exposure. Evaluation of chemical use profiles allows for the identification of exposure scenarios that may overlap, co-occur, or vary between chemicals, as well as for the identification of populations of concern.

Exposures to residential uses and in drinking water are incorporated into cumulative exposure assessments on a regional basis. EPA conducted 12 regional assessments for drinking water and residential exposures (they are found in Part IIA-L.). These regions coincide with USDA agronomic use regions, and reflect the differences in climate, soil conditions, and resulting pest pressures across the entire U.S. Exposure to OP pesticide residues in foods is considered to be uniform across the nation (i.e., there are no significant differences in food exposure due to time of year or geographic location). The single national estimate of food exposure was combined with region-specific exposures from residential uses and drinking water. The assumption of nationally uniform food exposure is based on data indicating that, to a large extent, food is distributed nationally and food consumption is independent of geographic region and season. Furthermore, patterns of pesticide residues from monitoring data provide little evidence for seasonal or geographic variation.

All of the dose-response characteristics (i.e., relative potency factors and points of departure), exposure data, and exposure scenarios must be combined in a manner to produce a logical outcome consistent with exposures likely to be encountered by the public in location and time (seasonally). EPA used Calendex™, a computer software program, to integrate various pathways while simultaneously incorporating the time dimensions of the data. Calendex provides a focused, detailed profile of potential exposures to individuals across a calendar year. The approach for each pathway of exposure and results for the OP cumulative risk assessment are explained below.

The food component of the OP cumulative risk assessment is considered to be highly refined because it is based on residue monitoring data from the USDA's Pesticide Data Program, supplemented with information from the Food and Drug Administration (FDA) Surveillance Monitoring Programs and Total Diet Study. The PDP data provide a very reliable estimate of pesticide residues in the major children's foods. They also provide direct measures of co-occurrence of OPs in the same sample, alleviating much of the uncertainty about co-occurrence in foods that are monitored in the program. PDP samples with non-detectable residues were treated in this assessment as "zero" values. The alternative approach of assigning values for non-detectable residues was demonstrated previously to have only negligible impact on the Margins of Exposure (MOEs) at the upper percentiles of exposure. (MOEs describe how far away the exposure is from the point at which the chemical begins to have effects. Risk concerns decrease with increasing MOE values.) Only residue data from composite samples were utilized in this assessment. For those foods not monitored in PDP, similar commodities that are measured by PDP served as surrogate data sources. This approach is considered to be reasonable and generally sound given that it is based on the concept that families of commodities with similar cultural practices and insect pests are likely to have similar pesticide use patterns and residue levels.

Another important aspect of the food exposure assessment is that it is based on actual consumption data from the USDA's Continuing Survey of Food Intakes by Individuals, 1994-1996 + 1998 (CSFII). The CSFII provides a detailed representation of the food consumption patterns of the US public across all age groups, during all times of the year and across the 48 contiguous states. In this survey, 20,607 individual participants were interviewed over two discontinuous days. The data were supplemented by the 1998 survey of 5,559 additional children from birth through 9 years old. For this preliminary assessment, the following age groups were analyzed: 1 through 2 years of age; 3 through 5 years of age; 20 through 49 years of age; and 50 years of age and greater. These age groups were selected because other age groups are rarely shown to be the most highly exposed in single-chemical assessments. OPP plans to perform additional analyses before reaching specific conclusion about risks associated with exposure to OPs via food. 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.

Exposures in drinking water to individuals are incorporated into the cumulative exposure assessment on a regional basis. The regional water exposure assessments conducted are considered representative of exposures from typical OP usage in one of the more vulnerable surface watersheds in each of the 12 regions evaluated. The assessment focuses on areas where combined OP exposure is likely to be among the highest within each region as a result of total OP usage and vulnerability of drinking water sources. The co-occurrence of OP residues in water is primarily estimated from modeling. Monitoring data are not available consistently enough to be the sole basis for the assessment. However, monitoring data are used to corroborate the modeling results. The estimated residues for each region represent typical pesticide uses and reflect seasonal variations as well as regional variations in cropping and OP use. This analysis represents a major step forward because it is based on a probabilistic modeling approach that considers the full range of data and not a single high-end estimate. OPP is confident that these estimates represent reasonable approximations of pesticide concentrations in water. The results of the OP cumulative risk assessment indicate that drinking water is not an important contributor to the total risk. The contribution from drinking water is one to two orders of magnitude lower than the contribution from OPs in food at percentiles of exposure above the 95th percentile for all population subgroups evaluated. This result is consistent for all the regions evaluated.

Applications of OP pesticides in and around homes, schools, offices, and other public areas may result in potential exposure via the oral (due to hand-to-mouth activity by children), dermal, and inhalation routes. There are few remaining residential uses of OPs as a result of risk mitigation over the last several years. Ten OPs were considered in the residential/non-occupational exposure pathway assessment. The current assessment is based on a probabilistic approach. Several reliable data sources were used to define how pesticides are used, dissipation of pesticide residues, how people may come into contact with pesticides (e.g., via dermal or inhalation exposure), and the length of time people might be exposed based on certain activities (e.g., playing on a treated lawn). Like drinking water, the residential exposure assessment is conducted on a regional basis and also reflects seasonal variations. The contribution from exposure to DDVP from certain indoor uses (“No Pest Strip” and crack and crevice treatment) have resulted in the lowest total margins of exposure. This observation is consistent for all 12 regions evaluated. In evaluating all three pathways, at the higher percentiles of population exposure, residential uses appear to be the major source of exposure. In particular, exposure from hand-to-mouth activity by children and inhalation exposure are the most significant contributors to the exposure of all age groups. These patterns occur for all population sub-groups, although estimated risks appear to be higher for children than for adults regardless of the population percentile considered.

In conclusion, the results of the preliminary OP cumulative risk assessment indicate that drinking water is not a major contributor to the total cumulative risk. Additional sensitivity analyses are needed on the upper percentiles of the exposure distribution for the food assessments before firm conclusions are reached. For the residential exposure pathway, those regions with the lowest total margins of exposure at the upper percentiles in the exposure distribution generally reflect the contribution of the inhalation route resulting from the indoor uses of DDVP. The results of the current assessment provide a highly refined, health protective estimate of the cumulative risk to the U.S. public from the use of OPs.

Table 1. Organophosphorus Pesticides Considered in the Preliminary Cumulative Risk Assessment*

Pesticide	Food Exposure Pathway	Drinking Water Exposure Pathway	Residential/Non-occupational Exposure Pathway
Acephate	✔	✔	✔
Azinphos-methyl	✔	✔	
Bensulide		✔	✔
Chlorethoxyfos		✔	
Chlorpyrifos	✔	✔	
Chlorpyrifos-methyl	✔		
Disulfoton	✔	✔	✔
Diazinon	✔	✔	
Dichlorvos (DDVP)	✔	✔	✔
Dicrotophos		✔	
Dimethoate	✔	✔	
Ethoprop	✔	✔	
Fenamiphos	✔	✔	✔
Fenthion			✔
Malathion	✔	✔	✔
Methamidophos	✔	✔	
Methidathion	✔	✔	
Methyl parathion	✔	✔	
Mevinphos	✔		
Naled		✔	✔
Oxydemeton-methyl	✔	✔	
Phorate	✔	✔	
Phosolone	✔		
Phosmet	✔	✔	
Phostebupirim		✔	
Profenofos		✔	
Pirimiphos methyl	✔		
Terbufos	✔	✔	
Tetrachlorvinphos			✔
Tribufos	✔	✔	
Trichlorfon			✔

*Exposure to pet uses was not included in the cumulative risk assessment because mitigation efforts are ongoing.