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A CASE STUDY OF THE CUMULATIVE RISK OF 24 ORGANOPHOSPHATE PESTICIDES

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FIFRA SAP Session Chair
FIFRA/Scientific Advisory Panel
Date: May 8, 2001

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Olga Odiott, M.S.
Designated Federal Official
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Federal Insecticide, Fungicide, and Rodenticide Act

Scientific Advisory Panel Meeting
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A Case Study of the Cumulative Risk of 24 Organophosphate Pesticides

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Tom Gilding, on behalf of the American Crop Protection Association

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INTRODUCTION

The Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), Scientific Advisory Panel (SAP) has completed its review of the set of scientific issues being considered by the Agency regarding a case study of the cumulative risk from 24 organophosphate pesticides. Advance notice of the meeting was published in the *Federal Register* on November 3, 2000. The review was conducted in an open Panel meeting held in Arlington, Virginia, on December 7- 8, 2000. The meeting was co-chaired by Ronald J. Kendall, Ph.D. and Stephen Roberts, Ph.D. Ms. Olga Odiott served as the Designated Federal Official.

The case study illustrated data use and the process for integrating multi-pathway exposures to 24 organophosphate pesticides from food, drinking water and residential sources. The topic was divided in four sessions: (1) Cumulative risk assessment method for dietary (food) exposure, (2) Cumulative risk assessment for residential exposure, (3) Cumulative risk assessment for drinking water, and (4) Integrated cumulative risk assessment. The first three sessions illustrated how the Agency applied the principles described in the exposure sections of the cumulative risk assessment guidance to monitoring data for residues of organophosphates on food and water. Available surrogate data on residential/institutional uses was used to estimate cumulative exposures/risk using the Relative Potency Factor Method as reviewed by the FIFRA SAP in September, 2000. An illustration of an approach to integrate exposures from the three pathways into a complete cumulative assessment was presented in session 4.

CHARGE

The specific issues addressed by the Panel are keyed to the background document, " A Case Study of the Estimation of Risk from 24 Organophosphate Pesticides" dated November 9, 2000, and are presented as follows.

SESSION I: CUMULATIVE RISK ASSESSMENT METHOD FOR DIETARY (FOOD) EXPOSURE

Question 1 The organophosphate pesticide (OP) case study uses Pesticide Data Program (PDP) monitoring data only. Data for pesticide residues in foods from market basket surveys and FDA data are of similar quality and reflect the co-occurrence of multiple OPs. The Office of Pesticide Programs (OPP) considers it reasonable to combine these types of data in as much as they reflect similar data quality. However, these data sets combined reflect only a limited number of crops. How might data from field trials that are designed to reflect exaggerated use rates (maximum application rates and minimum pre-harvest intervals) be adjusted to reflect a more realistic estimate of pesticide residues to which the public is likely to be exposed?

Question 2: The use of surrogate data and translation of residue data between crops with similar pest pressures and agronomic practices is common across commodities in single pesticide assessments. Under what practices can this approach be applied to multi-chemical assessments?

Question 3: PDP and market basket surveys implicitly reflect usage of pesticides for the crops for which they are available and the co-occurrence of pesticides in those commodities. However, for commodities for which these types of data are not available, no direct measure of co-occurrence is available. OPP has considered assuming the independence of pesticide use weighted for the percent of the crop treated. What alternatives can the Panel suggest to estimate co-occurrence when direct measures are not available?

SESSION II: CUMULATIVE RISK ASSESSMENT FOR RESIDENTIAL EXPOSURE

Question 4: Current methods for estimating residential exposures to single chemicals in residential settings rely upon the use of standard values derived from the literature or from studies submitted in support of pesticide registration. This approach was applied to the current cumulative case study, relying upon use instructions to determine the frequency, period of re-treatment, rate of pesticide application, and dates of onset and discontinuance of use. No information is available for estimating likelihood of co-occurrence of pesticides in a residential setting. Is the adaptation of this single chemical assessment approach to a multi-chemical assessment reasonable? What aspects of this approach are appropriate? What aspects of this approach require development of better data?

Question 5: Distributions of exposure parameters were introduced into the residential assessment in this case study, but only in the form of uniform distributions due to data limitations. OPP has little experience in the use of distributional analyses for residential exposures. What guidance can the Panel provide for determining the appropriateness of using point estimates, uniform distributions, and fitted distributions?

Question 6: Many data types are needed to improve the accuracy and precision of residential cumulative assessments. What types of data would be the most useful to further the ability to develop reasonable estimates of cumulative risk from residential use of pesticides?

SESSION III: CUMULATIVE RISK ASSESSMENT FOR DRINKING WATER

Question 7: Current modeling procedures for estimating pesticide residues in drinking water rely upon a clear understanding of pesticide use patterns for agricultural and urban uses. In the absence of these data, it may be possible to back calculate use rates in urban environments from water concentration data and urban density data. This process was used in the current case study to estimate contribution from urban use. Is this approach a reasonable method for estimating urban use for the purposes of modeling water concentrations as a function of pesticide use? What alternative methods for estimating urban use of pesticides might OPP consider?

Question 8: Assuming that the WARP model is adequately developed for use in risk assessments, is the approach taken in this example of a cumulative case study to incorporate exposure through drinking water appropriate? Can the Panel make any suggestions for improving the method by which drinking water is incorporated in cumulative assessments, given the limited availability of monitoring data?

Question 9 In the case study, the 95^{th} percentile upper bound prediction interval on the 95^{th} percentile concentration estimate was used as the basis for year round estimates of pesticide exposure in drinking water. This approach was adopted because available estimates of concentrations of pesticides in drinking water are annualized, with no indication of seasonal variation. Is this approach a reasonable, health protective approach? What is the potential for this approach to underestimate short term exposure? If this approach produces an exceedance of essentially safe exposure levels, in what manner could a better estimate of exposure to pesticides in water be derived from existing data and modeling approaches?

SESSION IV: INTEGRATED CUMULATIVE RISK ASSESSMENT

Question 10: The case study demonstrates the combination of data for food, water and residential exposures that reflect differences in the quantity of available data. Does the Panel have any concerns about combining data for different exposure sources that differ in the extent to which they describe anticipated real world exposures?

Question 11: In the current integrated case study, the contribution of water relative to other sources of exposure is very small. This pattern was evident from the initial single source assessment that preceded the integrated cumulative assessment. This approach could be used as a form of sensitivity analysis to simplify of the overall assessment. Can the Panel recommend any considerations in determining the extent to which minor contributors to risk can be eliminated from an integrated cumulative risk assessment? Generically, can the Panel identify any major concerns or pitfalls in this approach?

Question 12: The cumulative assessment in the case study was limited in geographic scale to the Piedmont areas of Virginia, North Carolina, and South Carolina in an attempt to focus the scale of the assessment on an area of consistent seasonal variation and pest pressure. In this way, OPP hopes to develop an integrated assessment within which the water and residential uses are relative constant, making the risk assessment relevant for that particular area and other areas like it. Does the Panel find the geographic scale to be appropriately limited such that the results of the risk assessment are applicable across the entire area? What considerations should OPP apply to define the appropriate geographic scale for drinking water and residential cumulative risk assessments? Does the Panel see major pitfalls to this approach?

Question 13: The data used in single chemical assessments often contains many sources of overestimation bias. However, because the cumulative risk assessment is developed from combining data from many sources and describing many pesticides, concerns for compounding conservatism is greater than for single chemical assessments. In the current case study, OPP has taken the approach of depending to the extent possible on monitoring data which most closely approximates real world exposures and has applied the value of zero where no detectable residues were available for food residues. Are these conventions reasonable given the complexities and uncertainties inherent in combining many data sets to develop an integrated, multi-chemical, multi-pathway risk assessment?

SUMMARY OF PANEL RECOMMENDATIONS

The Panel commended the Agency for making substantial progress in presenting a case study that includes various exposure analyses using different assumptions.

Dietary (food) Exposures

The Panel noted that for dietary exposure analysis, mixing the use of monitoring data and field trial data and tolerances tends to skew the analysis. A closer look at the residue monitoring data now becoming available for processed foods (e.g., in the PDP program) may enable the establishment of secondary adjustment factors for some processed foods for use in the DEEM analysis.

A distinction should be made in terms of when the tolerance and field trial data may be reasonable for use in a dietary exposure analysis. As long as it is possible for foods to contain residues at the tolerance level, it is reasonable to question the risk of consuming a single commodity at the tolerance level within a single day. The on-going effort to avoid using the tolerance and field trial data should not completely divert attention from addressing the reasonable scenario of an individual consuming a single commodity containing residue at the tolerance level.

Based on the Agency's presentation, translating data between crops does not appear to make noticeable difference to the high end exposure. Instead, data translation would likely make more significant difference for chronic exposures.

To address the lack of data, the Panel recommended analysis of the existing residue database and analysis of the pesticide use and sale data . The existing residue data could be analyzed for any pattern of co-existence of multiple pesticides that are present in commodities within a same crop group. The existing residue data could also be analyzed according to point of origin and the location of sampling. Data on pesticide use and sale, coupled with data on planting and harvesting acreage could be used to find any possible linkage among commodities from the same crop group. Another approach could be to find coordination between the sale and use data and the residue data for commodities within the same crop group. This type of comparison could serve as a support and a form of validation for the current use of pesticide use data.

The Agency's analysis showed that there is a significant portion of exposure from commodities that are not included in this case study. These are commodities with neither residue monitoring data nor data for commodities in the same crop group for data translation. Data for similar crops are also missing. Patterns of residue levels should be monitored for these crops.

Residential Exposures

Regarding the residential exposure session of the case study, the Panel was impressed with the quality of the case study but had several suggestions they felt would improve its quality and scientific rigor. The Panel noted that the case is too complex to be presented only in text format and suggested the inclusion of a summary table to improve the clarity and transparency of the report. The Panel emphasized the need to maintain consistency and transparency in the data, results, and throughout the assessment process to maintain the credibility of the process.

The Panel agreed that adaptation of the single chemical assessment approach to a multi-chemical assessment is reasonable. Some Panel members felt that the choice and timing of applications, while not a conservative approach, was both rational and logical.

The Panel agreed that there is a need to obtain data on residential co-occurrence of pesticides, including not only co-use inside the home, but also the combination of household use and residential/agricultural uses outside the home. However, it should be determined whether the possible patterns could appreciably alter the results of the cumulative assessment. To use the risk-analytic techniques available to determine whether such patterns could make a substantive difference in the total exposures, analysts would need to postulate the range of possible patterns one might observe among the various chemicals. The Panel suggested that closer collaboration between the Agency and industry would aid in developing a rational and realistic assessment of these processes. If it turns out that additional data collection about co-occurrence would be necessary to obtain reliable estimates of cumulative exposures, analysts would be in a better position to specify exactly what additional data are worth collecting.

There was debate among members of the Panel about whether it is reasonable to rely on label instructions to form the assumptions of the residential exposure assessment, or whether it might be prudent to consider actual practice of consumers when modeling uses and therefore exposures. The Panel noted that how well humans follow written instructions is well documented. If the Agency decides to consider the effects of over-application and misapplication, it would be useful to consult the literature describing human factors research.

The Panel suggested a three-stage process to gather information on residential use of pesticides. In the first stage, use instructions and data on pest cycles in the region would be used to determine frequency, period of re-treatment, and dates of onset and discontinuance of use. In the second stage, statistical surveys of consumers could be focused on particular segments of the application year to determine actual use. In the third stage, label directions would be used to define the application method, application rate, and protective equipment used.

The use of distributional analyses for residential exposures should rely on firmly established and transparent criteria for both the modeling process and for methods of dealing with model uncertainty, model variability, and input uncertainty. This is important for the overall cumulative assessment process to be credible. Many of the same principles that have been incorporated into the assessments of food should be incorporated into residential assessments.

Given the multiple models, data sets, and analyses involved in developing cumulative assessments for OPs, the Panel largely agreed that instead of defaulting to point values for model parameters that are subject to a high degree of uncertainty, it would be prudent for the Agency to employ stochastic simulations over reasonable ranges of a uniform distribution. As additional observational data are accumulated, distributional parameters for the stochastic simulations can be refined.

The Panel identified six major issues that would be useful in improving the case study:

1) The residential dermal pathway is poorly characterized.

2) Identification of special populations (e.g., children of agricultural workers) and other potentially high-risk populations via biomonitoring is needed.

3) National biomonitoring data in children and other specific exposure groups are needed for model evaluation.

4) Data on cross-media transfer, such as surface-to-food contamination, or pesticide uptake from water to food are needed.

5) Data on exposures in locations outside the home, such as schools and daycare centers, need to be addressed.

6) Animal data on the toxicokinetics of the pesticides could be evaluated for usefulness in regard to making linkages between exposure and dose. If no toxicokinetic data were available, then development of these data would be viewed as useful to develop a more refined estimate of cumulative risk.

Drinking Water Exposures

The Panel raised several issues concerning the accuracy of the Watershed Regression for Pesticides (WARP) model in predicting urban pesticide residues in drinking water as presented in the case study. Some of the Panel's recommendations for improvement follow.

1) The contribution of urban land use to its own drinking water supplies should be characterized. Specific to the case study, the patterns of urban use for chemicals T and P should be characterized.

2) Agricultural and urban basins would not differ systematically in precipitation, but they would differ in runoff. Including an indicator of runoff as an independent variable might make the estimate more accurate. Alternatively, considering the differences in chemical usage and transportation processes, the prediction errors may be reduced if separate equations are developed for the agricultural and urban land uses instead of one common regression equation.

3) The occurrence of high-intensity events (for example, a 2-year, 1-hour event) should be investigated as a dependent variable. A deterministic model such as PRZM/GLEAMS, which uses the curve number method to estimate runoff losses, can be used as an input variable to the regression model. Even though the PRZM/GLEAMS model may be quantitatively inaccurate and biased, it may provide a good *relative* pesticide loss estimate and therefore function well as an independent variable in the regression model.

Because of its conservatism, the drinking water assessment in the case study seems to provide a fairly convincing argument that drinking water is a relatively minor pathway for the two OPs considered. However, the method itself appears to have several shortcomings, the greatest being that it does not generalize to cases where this pathway may be more important. If predicted drinking water exposures are very large or peak at very high levels for other chemicals for which the method may be applied in the future, it will not be clear whether the predictions are high because there is a genuine danger of high exposures or merely because of the conservatism in the assessment.

The statistical approach that is taken is very conservative for simulation of drinking water contribution to OP exposure of individuals. By definition, simulating exposures for chemicals T and P at the population weighted 95% upper prediction limit predicts an overestimate for 95% of the population. Natural variation and simulation uncertainty should be reflected in the final inputs to the cumulative risk assessment. It is suggested that the uncertainty in the model predictions of cumulative risks be formally evaluated on the whole and not through fixing individual inputs at conservative assumptions.

The Panel noted the importance of accounting for temporal variability in drinking water concentrations. Drinking water contamination of pesticides could be rather localized, such as in an agricultural community or a "hot spot." Development of the model should include the capability to account for the temporal variations and for a smaller geographic scale.

Consideration of chemical degradation is particularly important for modeling the concentrations of breakdown products that are of toxicological significance. Incorporating information on chemical degradation through drinking water processing would further refine the model output.

The assumptions used in the case study for incorporating the WARP model output in the drinking water pathway of exposure appear to be conservative. The Panel recommended
1) direct measurement at the tap (surface and ground water systems) with time series throughout a several year period and 2) establishing the empirical distribution for simulations that apply to large regions. These data would provide valuable comparisons useful for model validation.

The Panel highlighted the need for a tool to model the level of pesticides in drinking water from ground water sources, the breakdown of pesticides through water processing, and any breakdown products of toxicological significance.

The Panel felt that it was limited in its capacity to advise on the appropriateness of use of the 95^{th} percent upper bound prediction interval based on the 95^{th} percent concentration estimates without studying the actual data.

There is a need to capture the temporal and geographic variations in assessing the exposure through drinking water. The Panel reiterated the realistic need to characterize the pattern of co-occurrence of multiple chemicals in the context of choosing an upper bound estimate for each chemical in the cumulative risk assessment.

The Agency should consider contacting other experts to explore the potential for use of models other than the regression approach presented. In light of current knowledge of available data and a better understanding of what is needed from the current model, other experts might be able to suggest additional approaches that are more transparent, less excessively conservative, and incorporate temporal and spatial components.

Whether the use of the 95^{th} upper bound prediction interval based on the 95^{th} percentile concentration estimate is health protective would depend on many factors (e.g., temporal, geographic location, inputs, and approach to model analysis, etc). Apart from all of these factors, and so far as modeling output is concerned, the 95^{th} upper bound prediction could be considered as reasonable for capturing the high-end values.

Integrated Cumulative Risk Assessment

The Panel commended the Agency for the integrated assessments presented in the case study, with all its current weaknesses, and putting the case study up for review. There is value to doing a modeling project even if all the information and data being used are not the best. The Panel concluded that the exercise itself raised the correct questions and issues.

In this case study, sources of exposure were identified for possible mitigation on the basis of their impact on the MOE at a given percentile. This method tends to pick out sources causing seasonal excursions, and it does not readily identify sources that are high contributors to exposure that do not vary over the year. Policy will have to be developed for determining which sources of risk should be mitigated.

Use of assumed, fixed values for samples that are non-detects or <LOD leads to artificial suppression of variance in input variables and can negatively impact subsequent uncertainty analysis.

The Panel noted that since it is inevitable that dissimilar data will be combined in an aggregate and cumulative analysis, uncertainty and variability should be distinguished. A 99.9 percentile from a 1-D analysis is much less defensible than an UCL of a lower percentile from a 2-D analysis.

Panel members expressed concerns about combining data from different sources, especially when there are LOD differences. Detected values may be swamped by LOD data in another part of the model.

Panel members also expressed concerns about combining data with quite differing levels of precision and conservativeness, and about the use of one set of data to drive other model considerations.

The model cannot be fully evaluated without real world (biomonitoring) data for comparison and that comparison cannot be made without 2-D representation of outputs. Biomonitoring data are highly recommended since it will enhance the credibility of the risk assessment.

Groundwater exposures should be included. Although groundwater exposure probably is not a major source in the case of OPs, it may be a significant contributor to the risk picture with some other pesticides.

One concern is why for pesticides C, T, and P used in crack and crevice treatments, only inhalation exposure was considered, particularly when the model assumes that pesticide C remains for 3 days unchanged in air concentration, and that T and P had active exposure periods of 30 days. The lack of inclusion of other routes of exposure biases the result toward inhalation. Several models presented elsewhere, which took into account other routes of exposure suggest that dermal and non-dietary routes of ingestion may play important roles for children.

The Panel was concerned that several contributors to exposure were ignored to reduced the analytical burden. The sum of minor contributors can, in some circumstances, be as large or larger than any major contributor. The Panel suggested two strategies to reduce the Agency's analytical burden: 1) narrow the population of interest and 2) use intervals rather than point estimates in the Monte Carlo simulations. This approach reduces the burden of data collection and parameterization and, although simpler than second-order Monte Carlo simulations, still distinguishes variability and uncertainty (i.e., incertitude or ignorance). Using intervals in a Monte Carlo simulation avoids creating a mix of partially probabilistic and partially deterministic estimates.

The Panel noted that the small geographic unit used in the model was excellent, well thought out, and appropriate.

For residential exposure, it is appropriate to try to define the geographic unit of analysis in terms of similar pest pressure.

Large ethnic minorities within a region that might have significantly different food consumption patterns from the general population should be examined.

The case study demonstrated the thought process behind choosing to use surrogate data versus not addressing a component of exposure due to lack of data. However, it is not reasonable to use a value of zero whenever residues are not detected. Using zeros does not automatically make an assessment more realistic. A blanket policy of replacing non-detects with zeros is an abdication of an important responsibility of the analyst. The professional judgement and rationale behind choosing zero concentrations when no detectable residues are available for food residues needs to be clearly articulated.

Close distributional approximation to real world systems should be the basis for simulating cumulative exposures and risks. Ideally, the inputs from each source and pathway should reflect stochastic variability that is representative of the real world.

DETAILED RESPONSES TO THE CHARGE

SESSION I: CUMULATIVE RISK ASSESSMENT METHOD FOR DIETARY (FOOD) EXPOSURE

Question 1 The organophosphate pesticide (OP) case study uses Pesticide Data Program (PDP) monitoring data only. Data for pesticide residues in foods from market basket surveys and FDA data are of similar quality and reflect the co-

occurrence of multiple OPs. The Office of Pesticide Programs (OPP) considers it reasonable to combine these types of data in as much as they reflect similar data quality. However, these data sets combined reflect only a limited number of crops. How might data from field trials that are designed to reflect exaggerated use rates (maximum application rates and minimum pre-harvest intervals) be adjusted to reflect a more realistic estimate of pesticide residues to which the public is likely to be exposed?

After years of monitoring pesticide residues in foods, a large reliable database exists on many commodities that are commonly consumed and commodities that are important to infants and children. While these commodity-specific data can be directly applied to dietary exposure analysis, a careful analysis of these data may also provide an inference of the residue patterns for those commodities whose residues have not been systematically monitored.

One possibility is to explore any pattern of actual residue levels relative to the tolerance. For example, the 1998 Pesticide Data Program (PDP) reported the "ratio of 90^{th} percentile to tolerance." For organophosphates, this ratio ranged from 0.001 to 0.05, meaning that the 90^{th} percentile residue is generally at 0.1 to 5% of the tolerance. Another useful pattern could be an expression of percentage of residues that comes within a step-wise percentage of the tolerance (e.g., the percentage of samples that contain residues at 1, 10, and 50% of the tolerance). When sufficiently established based on the actual residue monitoring data, these patterns may be useful for replacing the single point value from field trial data or the tolerance in a distributional analysis of dietary exposures.

In dietary exposure analysis, mixing the use of monitoring data and field trial data and tolerances tends to skew the analysis. The commodities having high contributions to the overall exposure are often those that are assumed to be at the tolerance. This is especially true for secondary residues, such as milk, poultry, and meat. In these cases, a careful analysis of the existing residue data could justify moving away from assuming residues at tolerance. For example, the 1998 PDP reported essentially non-detects in milk for most of the active ingredients. Such a pattern, when sufficiently established, could justify not using tolerance or field trial data as defaults, especially for analysis that includes multiple commodities and multiple chemicals.

The same could be said about adjusting residue data for processed foods. It appears that a closer look at the residue monitoring data now becoming available for processed foods (e.g., in the PDP program) may enable the establishment of secondary adjustment factors for some processed foods for use in the DEEM analysis.

A distinction should be made in terms of when the tolerance and field trial data may be reasonable for use in a dietary exposure analysis. In terms of pesticide food safety, one of the many remaining questions for tolerance assessment is whether food containing residues at the tolerance level is "safe." One aspect of the risk assessment approach to answering this question is to estimate the risk associated with exposure at the tolerance. As long as it is possible for foods to contain residues at the tolerance level, it is reasonable to question the risk of consuming a single commodity at the tolerance within a single day. In this analysis, one might want also to consider some background or average levels of exposure from other commodities that are not all at the tolerance. Compared to multiple- commodity, multiple- pesticide exposures, this type of analysis is simple, albeit necessary. In this case, assuming residues at the tolerance has a very different meaning than attempting to move entirely away from using tolerance or field trial data because it is highly improbable that all allowable commodities would contain residues at the tolerance. Thus, the on-going effort to avoid using the tolerance and field trial data should not completely divert our attention from addressing the reasonable scenario of an individual consuming a single commodity containing residue at the tolerance level.

Question 2: The use of surrogate data and translation of residue data between crops with similar pest pressures and agronomic practices is common across commodities in single pesticide assessments. Under what practices can this approach be applied to multi-chemical assessments?

This is a difficult question to answer. The Agency is commended for making substantial progress in presenting a case study that includes various exposure analyses using different assumptions. These presentations are very useful for the panel discussions. Based on the Agency's presentation, translating data between crops does not appear to make noticeable difference to the high end exposure. Instead, data translation would likely make more significant difference for chronic exposures.

It appears to be generally agreeable that residue data from one commodity could be used as a surrogate for another commodity within the same crop group. Essentially, this is the rationale behind establishing crop groups for the purpose of generating field trial data and for setting the tolerances for a single pesticide. In this case, the question is, what could the residue be if the same amount of pesticide is similarly applied (e.g., application methods, rates, pre-harvest interval) to another similar commodity (e.g., botanically, and agriculturally). When considering multiple chemical exposure the question becomes one of what and how many pesticides could be present in a commodity and at what level, when residue monitoring data are missing. One of the key considerations is the possible choices of pesticides that could be applied to this commodity. Another consideration is their possible application patterns (e.g., rates, pattern, methods) that would impact the residue levels.

For the lack of data, a very crude default could be to assume that the residue profile is the same for commodities within the same crop group. However, there would not be much support for this assumption. Two sources of information may be useful in predicting or estimating residues. One is the analysis of the existing residue database. The other is the analysis of the pesticide use and sale data.

The existing residue data could be analyzed for any pattern of co-existence of multiple pesticides that are present in commodities within a same crop group. There are several combinations of these commodities within the PDP program since 1991. For examples, apple and pear as pome fruits; celery, spinach, and lettuce as leafy vegetables (excluding *Brassica)*; orange and grapefruit as citrus; tomatoes and bell pepper as fruiting vegetables. There is also a question of how the pattern of multiple pesticides could vary geographically and temporally. The existing residue data could also be analyzed according to point of origin and the location of sampling.

Data on pesticide use and sale, coupled with data on planting and harvesting acreage would be another approach to finding any possible linkage among commodities from the same crop group. A simple application of this type of data could be an adjustment of surrogate residue data based on the percentage of crop treated. When applied to cumulative risk assessment, this would mean separately applying the pesticide-specific percentage of crop treated data to each pesticide in the mix. A further step could be to find coordination between the sale and use data and the residue data for commodities within the same crop group. This type of comparison could serve as a support and a form of validation for the current use of pesticide use data.

Since the dietary pathway is the most data-rich component of the pesticide exposure assessment process in EPA, the results of this type of data analysis may also provide insight on critical issues regarding cumulative risk assessment for other pathways of exposure.

The Agency's analysis showed that there is a significant portion of exposure from commodities that are not included in this case study. These are commodities (e.g., tree nut crops) with neither residue monitoring data nor data for commodities in the same crop group for data translation. Data for similar crops are also missing. It appears that patterns of residue levels would have to be monitored for these crops.

Question 3: PDP and market basket surveys implicitly reflect usage of pesticides for the crops for which they are available and the co-occurrence of pesticides in those commodities. However, for commodities for which these types of data are not available, no direct measure of co-occurrence is available. OPP has considered assuming the independence of pesticide use weighted for the percent of the crop treated. What alternatives can the Panel suggest to estimate co-occurrence when direct measures are not available?

Data analysis recommended under question 2 above may also provide useful information for the data extrapolation issue under this question. When the use or sale data are further lacking, PDP data could be analyzed for any prevailing patterns of co-occurrence of pesticides in a sample. For example, the 1998 PDP data showed 33.9% of fruits and vegetables containing more than one pesticide residue. Perhaps a pattern could be established in terms of the percentage of samples versus number of pesticides detected in a sample (e.g., percentage of samples containing 2, 3, or 4 pesticides, etc). For example, 1998 PDP reported "Samples vs. Number of residues detected per sample (Appendix k.)." Specific to the current case study, the focus would be only on the patterns of numbers of OPs in a sample. It may be possible that this information, coupled with the use database, could provide a bounding estimate of the probable numbers of pesticides that would likely co-exist in one commodity. For example, if 10 pesticides could be applied to one commodity, there may be a justification to limit the complexity of the dietary analysis to the top five pesticides. In terms of pesticide use data, it is understood that only the portion of the use data that could conceivably result in residues in foods is considered in the dietary exposure assessment. For example, the use of OPs during winter dormancy periods would not be included in the use database for characterizing the pattern of residues in foods.

SESSION II: CUMULATIVE RISK ASSESSMENT FOR RESIDENTIAL EXPOSURE

The Panel members were impressed with the quality of the case study, but had the following suggestions they felt would improve its clarity and scientific rigor.

The case study needs to maintain consistency and transparency in the data and results. This same principle of consistency needs to be applied throughout the assessment process. This is important in maintaining credibility of the process.

The estimates of exposure to children ages 1-3 are based on behavior patterns of older children that have been normalized to their dermal surface area or their weight. This is somewhat misleading to the reader and is a point that should be stated explicitly at the outset of the document. Children of different ages have different behavior patterns. Notably, infants (ages 0-1) have behavior patterns that would be expected to cause higher exposures. This is presumably the group that is at the greatest risk and should be explicitly considered. The Panel understands that such data are currently not readily available, but data should be collected to better quantify infant behavior. These data can be used with the same general approach to estimating exposure.

The case is too complex to be presented only in text format: a table summarizing stochastic and deterministic inputs (ideally there would be no deterministic inputs) would improve the clarity and transparency of the report as well. In a similar vein, values of margin of exposure (MOE) of zero in all figures in the Appendix are misleading. MOE is infinity in the absence of exposure. Furthermore, the MOE approach uses route-specific toxicity factors. Dermal toxicity translates relatively poorly because conditions of dermal exposure lack the physiological constraints present in the respiratory and gastrointestinal routes. Residence time in dermal assessment matters and is a function of behavior, and in this case animal models do not mimic human behavior well. The obvious desire to avoid route-to-route extrapolation is understandable, but the MOE approach may not be an improvement for dermal route effects. Lastly, ED_{10} and No Observable Adverse Effect Level (NOAEL) values in all figures in the Appendix lack units.

Groot et al. (1998), cited in the text on page 47, is not included in the references that begin on page 63. Kissel et al. (1998), cited on page 47 is a secondary reference and the primary reference should be cited. Primary information on the distinction between hand to mouth touching and insertion can be found by comparing Zartarian et al. (1997) with Zartarian et al. (1998).

Question 4: Current methods for estimating residential exposures to single chemicals in residential settings rely upon the use of standard values derived from the literature or from studies submitted in support of pesticide registration. This approach was applied to the current cumulative case study, relying upon use instructions to determine the frequency, period of re-treatment, rate of pesticide application, and dates of onset and discontinuance of use. No information is available for estimating likelihood of co-occurrence of pesticides in a residential setting. Is the adaptation of this single chemical assessment approach to a multi-chemical assessment reasonable? What aspects of this approach are appropriate? What aspects of this approach require development of better data?

Panel responses to these issues largely addressed the adequacy of the modeling approach, but they also touched upon inadequacy of some data and methods for collection of new data to improve assessments.

The Panel agreed that there is a need to obtain data on residential co-occurrence of pesticides. This includes not only co-use inside the home, but also the combination of household use and residential/agricultural uses outside the house. The current residential Standard Operating Procedure (SOP) assumes that exposure is a result of direct application of the pesticide to a surface such as a carpet, pet, rosebush, or lawn and a contact with the treated object or surface. The inclusion of outdoor uses is also important since there are ample data in the existing literature to indicate that infiltration from outdoors and track-in does occur and therefore residential exposure can come from these outdoor sources. In addition, there are data indicating that, after crack and crevice application, measurable amounts of pesticide are found on floors, surfaces, and objects located some distance from the areas of application. Clearly these are not residues in the same way that the term is used when discussing foliar residues or transferable residential residues from direct contact with a treated carpet.

The Panel agreed that adaptation of the single chemical assessment approach to a multi-chemical assessment is reasonable. Some Panel members felt that the choice and timing of applications, while not a conservative approach, was both rational and logical. These Panel members noted that there may be individuals who use multiple chemicals to blitz a flea infestation. For the majority of users, however, it is a reasonable assumption that for each application (fleas, shrubs, crack and crevice, etc.) only one chemical is applied.

The case study states that: “The PHED database takes advantage of the fact that, for many pesticides, the physical parameters of pesticide application methods and formulations have a greater impact on potential human exposure than the characteristics of the chemical itself.” One Panel member noted that factors other than those mentioned in this statement -- namely frequency, period of re-treatment, applications rates and date of application -- might significantly affect co-occurrence of pesticides. Co-occurrence most likely is associated with seasons for specific pests and formulations. For example, it is unlikely that pesticide users would spray for roaches at the same time the lawn is sprayed for chinch bugs. Data collection and modeling should examine the extent to which the serendipity of random scheduling of events leads to co-occurrence.

From a modeling standpoint one of the important issues identified by the Agency for estimating residential exposure is the probability of co-occurrence of pesticide applications. The software Calendex takes care of the effects of seasonality, the repulsed pattern of applications, and post-application re-exposures. However, it does not fully address the question of simultaneity of applications of different pesticides. As public comments from the American Crop Protection Association (ACPA) emphasized, a user wouldn't be expected to apply pesticide B if he has just applied pesticide A for the same pest. Counter factually assuming independence in such cases would overestimate exposures because it fails to take into account the negative correlation between different pesticides. In other situations there may be positive associations between pesticide applications. When professional exterminators visit a house for termites, they might also detect and treat for one or more other pests. Likewise, when the family pet contracts fleas, consumers sometimes use more than one anti-flea pesticide simultaneously or in very rapid succession. Thus, it may well be that assuming independence between some chemicals overestimates some cumulative exposures, while the same assumption between other chemicals underestimates other cumulative exposures.

However, before one worries about collecting data on the simultaneity or anti-simultaneity of pesticide applications, it may make sense to determine whether the possible patterns could appreciably alter the results of the cumulative assessment. There are risk-analytic techniques available that can be used to determine whether such patterns could make a substantive difference in the total exposures. If the old adage is "measure twice, cut once," we might offer a new version for risk analysis—where data collection is very expensive—as "think three times before measuring twice." The risk analysis techniques range from what-if studies to formal bounding assessments. To use these techniques, analysts would need to postulate the range of possible patterns one might observe among the various chemicals. As some of the public commenters pointed out, closer collaboration between the Agency and the industry on this assessment would aid in developing a rational and realistic assessment of these processes. Perhaps representatives from the industry groups would be willing to proffer some suggestions about how such co-occurrence patterns could be modeled. It may turn out that strongly disjointed patterns of occurrence for many chemicals and positively associated co-occurrence for other chemicals have negligible net effect on cumulative exposures (although this seems unlikely). If it turns out that additional data collection about co-occurrence would be necessary to obtain reliable estimates of cumulative exposures, analysts would be in a better position to specify exactly what additional data are worth collecting. In this case, it is likely that market share data will be important, but these data almost certainly will not tell the whole story.

The Agency also identified modeling human behavior as an important issue for this cumulative assessment. There was debate among members of the Panel about whether it is reasonable to rely on label instructions to form the assumptions of the assessment, or whether it might be prudent to consider actual practice of consumers in modeling uses and therefore exposures. Some panelists emphasized that a pesticide label constitutes a legal document and, although its instructions do not have the force of law for consumer behavior, they argued that it may be reasonable to presume that a rational consumer would nevertheless follow them carefully. Other Panelists were concerned that misapplications and over-applications could be significant, especially by children but also by illiterate, hurried, or merely inattentive adults, and this possibility should be considered in the Agency's assessment. If the Agency decides to consider the effects of over-application and misapplication, it would be useful to consult the literature describing human factors research. There is a great deal that is known about how well humans follow written instructions. By propagating misapplication rates (e.g., Millstein 1994; 1995), it would be possible to account for the resulting uncertainty about residential exposures. This uncertainty should then be incorporated into the uncertainty about the final cumulative exposures.

One Panel member pointed out that use of the assumption that pesticides are applied at label rates in the residential scenario leads to multiple undesirable outcomes: 1) The overall analysis represents a blend of probabilistic and deterministic inputs. This leads to underestimation of uncertainty which is a liability when results are to be interpreted. 2) Use of label rates in the residential scenario is internally inconsistent since the dietary exposures are based on measured values (resulting from application rates that undoubtedly do not always match label rates). 3) Assumption of label rates is inconsistent with realistic appraisal, which is the whole point of the probabilistic approach.

One Panel member noted that the rate of dissipation used in the residential case study seemed to be quite conservative. Whereas for most chemicals, available studies suggested little or no residue beyond 24 hours, the case study assumed Day 0 (sometimes Day 2) residue available and persistent for 7 days following application. Other Panel members noted that there are published data showing that measurable residues of some pesticides are present on surfaces after periods greater than 24 hours and that some semi-volatile compounds can redistribute onto non-treated surfaces within households.

In an ideal world, detailed information on residential use of all the target pesticides would be obtained from statistical surveys like the one being conducted by the Residential Exposure Joint Venture (REJV). The REJV survey will provide data on every pesticide application in the home over a full year. It will provide details on the amount of product applied, the method of application, what the applicator wore, and the time before the treated area was reentered. Unfortunately, this kind of survey is expensive to conduct, and the amount of effort required of respondents makes it somewhat doubtful that complete information will be obtained.

A three-stage process might be appropriate: In the first stage, use instructions and data on pest cycles in the region would be used to determine frequency, period of re-treatment, and dates of onset and discontinuance of use. This is what the Agency has done in the current document in constructing the Gant chart of application timing. In the second stage, statistical surveys of consumers could be focused on particular segments of the application year to determine actual use. In the third stage, label directions would be used to define the application method, application rate, and protective equipment used.

<u>Stage 1</u>   Using use instructions for the individual pesticides to determine frequency, period of re-treatment, rates of application and dates of onset and discontinuance of use is appropriate. OPP has used this information, along with data from the National Gardening Survey and the Certified/Commercial Pesticide Applicators Survey, to produce a Gant chart showing the timing of applications of seven pesticides used residentially throughout the year. Defining the domain of probable co-occurrences in this way is very reasonable.

<u>Stage 2</u>   In contrast to the REJV survey, the consumer surveys in Stage 2 would cover no more than 1-2 months of use per household, and would ask for more limited information. The reason for this is both to reduce cost and to increase the probability of getting complete information. Rather than ask for a lot of detail on each use, the surveys could ask only which product was used and when and to what it was applied. The major objective would be to get data on co-occurrence of uses. While it would be ideal to also find out *how* the pesticides are being used, it seems reasonable to sacrifice that in order to get good information on *what* and *when*. (Like the REJV, these surveys should collect basic demographic information on the household, as well as on characteristics of the property, including the areas of the house and lawn, presence of a vegetable garden, pool or pets, and the number of trees and shrubs.)

<u>Stage 3</u>   The application method, application rate, and protective equipment used for each use identified in a survey would be assumed to conform to product label directions, i.e., it would be assumed that consumers applied the products according to the directions.

<u>Stage 3a</u>   It would be ideal to have information on how consumers *actually* apply pesticides, because we know they do not do it according to label instructions. This information could be collected via observational studies, which could focus strictly on the *how* of residential use, without having to estimate the frequency and timing of uses.

Question 5:   Distributions of exposure parameters were introduced into the residential assessment in this case study, but only in the form of uniform distributions due to data limitations. OPP has little experience in the use of distributional analyses for residential exposures. What guidance can the Panel provide for determining the appropriateness of using point estimates, uniform distributions, and fitted distributions?

The use of distributional analyses for residential exposures should rely on firmly established and transparent criteria that are common to all distributional analyses. Many of the same principles that have been incorporated into the assessments of food, for example, should be incorporated into residential assessments. Not doing this results in assessment hybrids that are not consistent in approach and thereby likely underestimate uncertainty. In order to do this it is important to develop clear and consistent criteria for both the modeling process and for methods for dealing with model uncertainty, model variability, and input uncertainty. While this question deals only with input uncertainty, model uncertainty and model variability must be addressed systematically along with issues of input uncertainty for the overall cumulative assessment process to be credible.

This three-point framework for describing model variability and uncertainty is outlined in Cullen and Frey (1999), which is a useful guidebook and starting point for addressing the issues raised by this question. Once these principles are clearly articulated and inculcated into the case study, decisions based on application of this framework should be easier to justify.

Given the multiple models, data sets, and analyses involved in developing cumulative assessments for OPs, the Panel largely agreed that probabilistic methods are the preferred approach for estimating exposures and risks. In several cases, such as number of fingers in mouth, transfer from moist and dry hands, and saliva removal from hands, EPA reports a range of values used in the uniform distribution in its model. While not a perfect solution, this is better than point estimates. The use of uniform distributions, which are generally used in cases where data are sparse or inconsistent, are better than point estimates. Fitted distributions should be used when there is some underlying rationale, such as processes driven by physical parameters, such as vapor pressure or product formulation.

Using the uniform distribution is much less violent than using an assumption of independence of all variables in the model. It is the independence assumption that causes hyperconservativism in the tails when many variables are combined in an assessment. In a sense, using uniform distributions is better than using, for example, all normal or all lognormal distributions because it is clear to everyone that the uniforms are really only placeholders for more appropriate distributions that will be substituted when they can be properly parameterized.

There are essentially two options in a simple Monte Carlo simulation: (1) empirical distributions, which typically underestimate tail risks and (2) fitted distributions, which require specification of a distribution family but which allow the analyst to incorporate structural or mechanistic knowledge.

It is worth emphasizing that a uniform distribution is not the same thing as a plus-minus range or interval. When uncertainty consists mostly of incertitude (ignorance) rather than variability per se, this can be an important distinction in risk analysis.

The use of point values for model parameters will lead to attenuated variance in the final estimates of the total exposure and subsequent assessment of risk. Realistic model simulations require accurate data on the full distributional properties of each model parameter, e.g., application rates, frequency of application, human activity in affected areas, transfer rates, absorption, inhalation, ingestion, and relative potency. The documentation of the simulation results should identify the distributional assumptions employed. In the absence of observational data, stochastic inputs based on reasonable assumptions (i.e., uniform, non-informative) should be used. If minima and maxima are available from observational studies but the samples are not sufficiently large to estimate other distributional parameters, a uniform prior would be a conservative prior assumption for a Monte Carlo simulation. Why is the uniform conservative? — it thickens both tails and the true distributions over the range are likely to be skewed with long upper tails. The use of uniform distributional assumptions for multiple parameters can lead to extreme exposures if the simulated draws of concentrations for two co-occurring OPs were both extreme. Nevertheless, it would be prudent for the Agency to employ stochastic simulations over reasonable ranges of a uniform distribution rather than to default to point values for model parameters that are subject to a high degree of uncertainty. Use of minima and maxima based on small numbers of observations may not fully represent the extremes. Therefore, model developers and users may wish to extrapolate the uniform distribution bounds based on the sample size and the observed extremes. As additional observational data are accumulated, distributional parameters for the stochastic simulations can be refined.

Independent, replicated runs with stochastic inputs for each parameter will enable the user to estimate the simulation uncertainty (variance). It does not provide a measure of the bias associated with incorrect distributional assumptions. Measurement of bias in the cumulative risk assessment requires some external means of validating the model inputs or more directly the predicted exposures (e.g. biomonitoring data).

Question 6: Many data types are needed to improve the accuracy and precision of residential cumulative assessments. What types of data would be the most useful to further the ability to develop reasonable estimates of cumulative risk from residential use of pesticides?

The Panel identified six major issues that it felt would be most useful in improving the case study.

1) The residential dermal pathway is poorly characterized (as demonstrated by its sparse treatment in the case study). Available information on efficiency of surface-to-skin transfer processes is largely inadequate at present.

2) It is not clear from the presentation how special populations (e.g., children of agricultural workers) are to be covered. These populations are likely to be most in need of regulatory protection, if any is required. Identification of these and other potentially high-risk populations via biomonitoring is needed.

3) Data on cross-media transfer, such as surface-to-food contamination or pesticide uptake from water to food are needed.

4) Data on exposures in locations outside the home, such as schools and daycare centers, need to be addressed in the case study.

5) Sophisticated statistical approaches were proposed by several panel members to estimate residential exposure (as well as dietary and drinking water exposure). One panel member noted that little emphasis has been placed to date on the use of toxicokinetic models to transition from exposure to the internal dose at the target site. In the view of this panel member, it would not be the best use of limited agency resources to focus only on models for estimating uncertainty and variability in external exposure and ignore more biologically based models relating exposure to response. Toxicokinetics is, in some respects, a bridge between exposure and the critical interaction of the agent with the biological target that is assumed to be common to all the pesticides sharing a common mechanism of toxicity. Various approaches can be used to incorporate toxicokinetics from physiologically based toxicokinetic modeling to a simple comparison of biological half-lives of the various pesticides grouped under a common mechanism of action. Animal data on the toxicokinetics of the pesticides used to support their registration could be evaluated for usefulness in regard to making linkages between exposure and dose. If no toxicokinetic data were available, then development of these data would be viewed as useful to develop a more refined estimate of cumulative risk.

6) National biomonitoring data in children and other specific exposure groups are also needed for model evaluation. Along these same lines we also need to know more about OP metabolites (including oxons) in the environment and whether they are absorbed and metabolized.

Summary of Research in Progress

At the International Society of Exposure Analysis (ISEA) conference in October 2000, a number of studies were presented which will within the next year or two provide EPA with additional data beneficial to the risk assessment process. Gathering information about co-occurrence of pesticide applications would be valuable. Some up-to-date OP usage data for Georgia was reported at ISEA by MacIntosh and co-workers. There may be similar studies being conducted in other areas of the country.

Use of whole body dosimeters for children is currently being investigated by the Research Triangle Institute (RTI) and the Environmental and Occupational Health Sciences Institute (EOHSI). The results need to be compared with current adult dosimetry measures. There is a lot of excellent work coming out of the laboratories of Drs. Fenske and Kissel at the University of Washington. Dr. Kissel's work on dermal soil contact rates will be of great value in estimating exposure and risk for children. Further similar work needs to be done in other areas of the country to assure that the data obtained are representative of the larger population, or possibly to identify regional or cultural variations.

Studies by Dr. David Camann and his group at Southwest Research Institute will provide further information about the influence of saliva on pesticide adherence and removal, as well as on the dislodgability of a range of OPs from carpet. Apparently not all OPs behave the same way.

Studies from the Fred Hutchinson Cancer Research Center on children between 10 and 60 months old provide some interesting data on young children. These observations found that children less than 24 months old had very high rates of mouthing (76/hr for combined objects, hands, body parts, surfaces). The rates for older children (25-60 months) was half that of the younger children. Because of the difference in data collection methodology compared with that used by the group at Stanford (Zartarian et al. 1997 and 1998) and by the group at EOHSI (Reed et al. 1999), further work is needed to understand the differences in reported activities. It may be that the work of Zartarian and Reed, which is the basis of current EPA hand-to-mouth rates used in the exposure models, is an underestimate.

Additional data are needed on the sequencing of events between hand-to-mouth and object-to-mouth activities and on expanding our understanding of contact and transfer issues. For example, we have observed that most hand-to-mouth activities occur indoors during periods of reduced activity. Preceding those mouthing events, the child may have contacted surfaces and objects both indoors and outdoors with no hand washing prior to mouthing. We do not yet understand the amount and duration of pesticide adherence to hands from one event to another. The current models assume discrete events, with little perturbation of loadings from other activities. Without further data in this area it is unclear if this is a conservative model.

The assumption that one can combine exposures to pesticides that have adverse effects through a similar mechanism of toxicity also seems to assume that the pesticides behave similarly in the environment and have similar contact and transfer characteristics. This may not be the case. There are data indicating that how OPs behave on skin depends upon the polar characteristics of the pesticide and the moisture/sebum characteristics of the skin.

SESSION III: CUMULATIVE RISK ASSESSMENT FOR DRINKING WATER

Question 7: Current modeling procedures for estimating pesticide residues in drinking water rely upon a clear understanding of pesticide use patterns for agricultural and urban uses. In the absence of these data, it may be possible to back calculate use rates in urban environments from water concentration data and urban density data. This process was used in the current case study to estimate contribution from urban use. Is this approach a reasonable method for estimating urban use for the purposes of modeling water concentrations as a function of pesticide use? What alternative methods for estimating urban use of pesticides might OPP consider?

Previous Panels enthusiastically endorsed the use of regression models for this purpose, and it remains the most promising approach. The back-calculation of the pesticide use in urban areas is a common-sense approach. However, the Panel raised several issues concerning the accuracy of the WARP model in its urban prediction as presented in the case study. The Panel offers the following specific recommendations for improvement.

Drinking Water Contribution from Urban Use

A question is raised regarding the extent of contribution of urban land use to the drinking water contamination of pesticides at the same urban site. Specifically, the contribution of urban land use to its own drinking water supplies should be characterized. The understanding is that urban areas seldom consume their own runoff, and that most Community Water Systems (CWSs) are located upstream to urban areas. If this is not the case, the Agency and USGS should make targeted water monitoring in urban streams a priority. Specific to the case study, the patterns of urban use for chemicals T and P should be characterized. Crack and crevice use would presumably have much lower transport potential than lawn use.

Data Use in Modeling

The back calculation appears to be highly inaccurate. The regression equations for the agricultural uses, which are in turn used to back-calculate the urban uses, have an unacceptably low R^2 value (0.14) in the case of chemical P. This leads to the question concerning the accuracy of the estimation of the chemical use in the urban setting. The equation in Step 1 can be improved by considering additional factors to *use/basin area* and by developing a more complete regression model. Also, there should be an effort to use as many data as possible, because temporal variability is high from seasonal weather patterns. Instead of choosing to use single-year data, multiple years data from monitoring sites weighted by region should be used.

One criterion in selecting agricultural basins for developing the agricultural equation is high use of the target pesticide. If there is a positive relationship between use density and concentration, selecting only the upper range of use density will cause the regression slope to be underestimated (and the intercept overestimated). When the estimated regression equation is used to back-calculate use, use will be underestimated at low concentrations and overestimated at high concentrations. To avoid this, agricultural basins representing the full range of use rates should be used to develop the equation.

Model Construct

Based on the low R^2 values (0.63 and 0.43 for chemicals T and P, respectively) on log-log relations, the overall regression equations would have high prediction errors. The considerable variation in the independent variables in the two equations for the chemicals T and P is also a cause for concern.

The Panel members have misgivings about the method of back-calculating urban use density. The premise underlying the method is that concentrations coming off urban drainage basins are the *same* function of use density as for agricultural basins. There are a number of variables that reasonably must influence the concentrations coming off any drainage, including amounts of precipitation and runoff. That is, for any given use density, the resulting stream concentration will depend on precipitation and runoff. There is no reason to expect that agricultural and urban basins would differ systematically on precipitation, but they would differ in runoff. Urban basins are more heavily paved, and they have systems for quickly carrying runoff to streams. Including an indicator of runoff as an independent variable might make the estimate more accurate. Alternatively, considering the differences in chemical usage and transportation processes, the prediction errors may be reduced if separate equations are developed for the agricultural and urban land uses instead of one common regression equation.

Another issue is the use of combined variables (ppt-evap) in the regression. In most situations, this is typically a sign that the two variables are correlated and hence the regression is attempting to estimate the one parameter that represents the information from the two variables. Parameter estimates for such parameters would be quite variable. It is also noted that for chemical P, the variable (ppt-evap) has a negative coefficient, counter to expectation. Since the ppt-evap variable is a 30-year average, and that pesticide movement is largely driven by few extreme hydrologic events, it is advisable to use the actual weather data of the monitoring years as an independent variable.

It is also suggested that the occurrence of high-intensity events (for example, a 2-year, 1-hour event) be investigated as an independent variable. It may be worthwhile to investigate whether a deterministic model such as PRZM/GLEAMS, which uses the curve number method to estimate runoff losses, can be used as an input variable to the regression model. Even though the PRZM/GLEAMS model may be quantitatively inaccurate and biased, it may provide a good *relative* pesticide loss estimate and therefore function well as an independent variable in the regression model.

Confidence Bounds

It is noted that the selection criteria presented in the case study for reflecting agricultural and urban sites are very different. For the agricultural sites, the criteria are low population density (<50 persons/km^2), low percentage of urban land (<5%), and high use of the selected pesticide (>0.2 kg/km^2 for Chemical T and >1 kg km^2 for Chemical P). The regression model is used to predict the 15 urban sites for Chemical T with <0.01 kg/km^2 agricultural uses, 40-100% urban land, and population densities of 330-1700 persons/km^2. The wide confidence bounds associated with this extensive extrapolation could potentially mean very conservative estimates of water concentration and result in overestimated exposure.

Uncertainties are also introduced in the series of steps in the back calculation, as presented in the case study. The process allows an estimate of the urban application rate which is then added to the agricultural application rate to produce the total use, which is converted by natural log to an area-adjusted use intensity value, which is then used as a predictor in another regression model to predict stream concentrations. It is suggested that the upper prediction limits could be improved by incorporating the uncertainties from the initial regression used to predict the urban use intensity value.

How tight are the first stage and second stage regressions? From figure 6-2, the R^2 appears to be about 0.8. Confidence intervals based on jackknife or bootstrap techniques applied to the regressions might produce better confidence intervals for the next level.

Question 8: Assuming that the WARP model is adequately developed for use in risk assessments, is the approach taken in this example of a cumulative case study to incorporate exposure through drinking water appropriate? Can the Panel make any suggestions for improving the method by which drinking water is incorporated in cumulative assessments, given the limited availability of monitoring data?

The Agency is complimented on its effort so far in the cumulative assessment of OPs. Overall, the work represents a substantial and important advance in the regulatory practice of risk assessment. The WARP model represents a reasonable progression from the previous simpler screening models.

The cumulative risk assessment described in this example was a population-averaged risk assessment which should be distinguished from assessment of individual risk. The nature of drinking water exposures (the common community source) closes the gap between population-averaged and individual extreme risks. The processes through which OPs enter drinking water and are removed through treatment attenuate the extremes and integrate over the whole range of uses. Given the empirical data and the case study results for Chemicals T and P, the potential exposures did not appear to dominate the cumulative risk assessment.

Question 8 asks the SAP about the appropriateness of the approach assuming that the WARP model is adequately developed for use in risk assessments. This is a big assumption however, and the Panel provided several recommendations in this area. The use of the WARP model is probably the least secure aspect of the assessment.

Scope of Case Study

Because of its conservatism, the drinking water assessment in the case study seems to provide a fairly convincing argument that drinking water is a relatively minor pathway for the two OPs considered. But this question from the Agency is asking about the *method* used in the assessment rather than its particular conclusions. The method itself appears to have several shortcomings, the greatest being that it does not generalize to cases where this pathway may be more important. The conservatism in the assessment method seems to be very strong. If it happens that predicted drinking water exposures are very large or peak at very high levels for other chemicals for which the method may be applied in the future, it will not be clear whether the predictions are high because there is a genuine danger of high exposures or merely because of the conservatism in the assessment. In this case, without relevant monitoring data or special model validation, there will likely be much contention about whether the predictions represent prudent assessments.

Statistical Issues

It is important to ask whether the analysis uses statistically sound methods and reasonable assumptions. There are several issues where this seems in doubt. It is not expected that the 95th percentiles would be normally distributed. Certainly the 99.9th percentiles that the NRDC suggests using are not likely to be normally distributed. Analysts should consider modeling such values with extreme value theory, which is the traditional tool in this context. What is really needed is a fully distributional approach. After all, the 95th percentile is not unrelated to the 90th or the 99th. It is strange statistically to model these separately, and it is hard to believe that a different approach would not be better.

The statistical approach that is taken is very conservative for simulation of drinking water contribution to OP exposure of individuals. By definition, simulating exposures for chemicals T and P at the population weighted 95% upper prediction limit predicts an overestimate for 95% of the population. Natural variation and simulation uncertainty should be reflected in the final inputs to the Cumulative Risk Assessment. It is suggested that the uncertainty in the model predictions of cumulative risks be formally evaluated on the whole and not through fixing individual inputs at conservative assumptions.

It is noted that, given 101 data points and five explanatory variables (such as used for chemical P), the regression model comes very close to violating Occam's Razor. The fifth root of 101 is less than three, suggesting the regression has rather limited reliability. When censoring (non-detects) becomes more prevalent, as it no doubt will for other OPs and in other assessments for chemicals with other modes of action, the problem of sparse data will become even more worrisome.

Geographic and Temporal Considerations

Given the strongly structured nature of drinking water origin, contamination and consumption through time and across space, it also seems rather strange to use a completely structureless regression model. Would it not be feasible to use some kind of kriging or spatially explicit regression approach?

Perhaps even more important is the need to account for temporal variability in drinking water concentrations. This approach might also focus on the relatively rare but perhaps toxicologically significant extreme events associated with spring or seasonal runoffs. Drinking water contamination of pesticides could be rather localized, such as in an agricultural community or a "hot spot." For surface water, it is also expected that the pesticide concentration would vary temporarily, according to the season of use. It is therefore desirable to include in the development of the model the capability to account for the temporal variations and for a smaller geographic scale. It is encouraging that WARP has the capability to model as small as a 50-square kilometer area.

The Panel's answer to Question 9 describes what may be a much more reasonable temporally explicit approach to modeling drinking water concentrations. One issue to keep in mind in using such an approach is the need to pay attention to co-occurrence data. Especially if the Agency plans to combine 95% levels for all 24 OPs, it will be essential to account for the observed co-occurrence patterns.

Population Weighted Distribution

An alternative to the population weighted distribution of water concentration in the simulation as presented in the case study is population weight draws from the pool of available concentration observations with weights assigned to observed CWS data sets established based on water shed characteristics. Time of year should be factored in if the time-dependent sample sizes are sufficiently large. Population weighting of exposure draws is an important feature of the simulation for a defined human population.

Chemical Fate and Toxicological Considerations

A cumulative assessment needs to more realistically estimate the fate of the chemicals in drinking water systems, which in most (but not all) cases involves some residence in a reservoir (with highly variable residence times). This factor needs to be included into the distribution of concentrations, which would require a connection between the stream and the drinking water system for each region under consideration (the mid-Atlantic/Piedmont region in this case). EXAMS may be employed for this. Also, more information needs to be included on the effect of water treatment and, again, the distribution of concentrations.

Consideration of chemical degradation is particularly important for modeling the concentrations of breakdown products that are of toxicological significance. For organophosphates, some oxidative degradation products have substantially greater toxicity than the parent compounds. The case study models the pesticide levels at the point of surface water intake. Incorporating the information on chemical degradation through drinking water processing would further refine the model output to more closely represent the forms and levels of pesticide residues at the point of consumption.

Drinking Water Monitoring

The assumptions used in the case study for incorporating the WARP model output in the drinking water pathway of exposure appear to be conservative. Quality monitoring data would provide valuable comparisons useful for model validation. Recommendations were made for 1) direct measurement at the tap (surface and ground water systems) with time series throughout a several year period and 2) establishing the empirical distribution for simulations that apply to large regions.

It should be noted that, at realistic sampling intensities, this approach does not have the ability to identify hot spots. Stratification as discussed in previous SAP meetings would help to improve the efficiency of the samples. Data of the type presented by Dr. Tierney during the public comment period could help define the utility of direct observation data.

Ground Water Data

The Panel highlighted the need for a tool to model the level of pesticides in drinking water from ground water sources, the breakdown of pesticides through water processing, and any breakdown products of toxicological significance.

Question 9 **In the case study, the 95th percentile upper bound prediction interval on the 95th percentile concentration estimate was used as the basis for year round estimates of pesticide exposure in drinking water. This approach was adopted because available estimates of concentrations of pesticides in drinking water are annualized, with no indication of seasonal variation. Is this approach a reasonable, health protective approach? What is the potential for this approach to underestimate short term exposure? If this approach produces an exceedance of essentially safe exposure levels, in what manner could a better estimate of exposure to pesticides in water be derived from existing data and modeling approaches?**

The Panel is limited in its capacity to advise on the appropriateness of use the 95th percent upper bound prediction interval based on the 95th percent concentration estimates without studying the actual data. How much do urban application rates drive the 95th percent confidence interval on the 95th percentile concentration estimates? How likely would the temporal patterns produce low annual mean concentrations but with high temporal variance?

The Panel offered several points of consideration within the context of the case study. The Panel members feel strongly about the need to capture the temporal and geographic variations in assessing the exposure through drinking water. These are important factors in determining acute and cumulative exposures. In addition, the Panel reiterated the realistic need to characterize the pattern of co-occurrence of multiple chemicals in the context of choosing an upper bound estimate for each chemical in the cumulative risk assessment.

One suggestion for estimating the confidence bounds is to work with the median estimates, carry variance information forward, and build in confidence estimates later. Chemical transport is strongly affected by seasonality, especially with OPs, and the concentrations may be much higher during short time periods during the predominant time of application, especially if associated with an extreme hydrologic event (unusually heavy rains). The assumption that the 95th percent bound occurs every day may therefore not be a very conservative estimate, especially because the prediction errors appear to be higher with high concentrations, and should perhaps be the focus for further investigation.

It is expected, however, that OPs have a more even distribution than atrazine during the growing season, because they tend to be applied more evenly (although the general fate properties, especially high Koc values, would suggest greater runoff potential). On the other hand, some of this may be evened out if the CWS involves a basin with long residence time. Again, it appears advisable to try to incorporate temporal factors into the assessment procedure and to develop distributions that include these factors. It is suggested that, as a first step, the seasonal variability for OPs in the NAWQA database be investigated. Also, the co-occurrence should be evaluated (ACPA studies suggest that this is minimal).

The WARP regression model should not be applied to quantiles of the distribution for a year but to the actual time-dependent sample observations that are used to compute —specifically the rich database of individual OP concentration levels measured at multiple sites and points throughout the year. The model would factor in time (possibly collapsed to months or weeks) to reflect the seasonal variations that occur across measurement sites. Fixed effects including watershed area and soil characteristics, application rates, and rainfall would still be included in the model; however, the seasonally varying inputs such as rainfall, temperature, and application schedules would be included as time dependent covariates in the model. Since this model would include repeated measurements of concentrations at CWS sampling sites with time dependent covariates (e.g., rainfall amounts, application schedules), a general linear mixed model (SAS PROC MIXED) should be used to estimate the model parameters.

The Agency should consider contacting other experts to explore the potential for models other than the regression approach presented. In light of current knowledge of available data and a better understanding of what is needed from the current model, other experts might be able to suggest additional approaches that are more transparent, less excessively conservative, and incorporate temporal and spatial components.

Thus, whether the use of the 95^{th} upper bound prediction interval on the 95^{th} percentile concentration estimate is health protective would depend on many factors, some of which are those mentioned above (e.g., temporal, geographic location, inputs and approach to model analysis, etc). Apart from all these factors, and so far as modeling output is concerned, the 95^{th} upper bound prediction could be considered as reasonable for capturing the high-end values. For acute exposures, the use of 95^{th} upper bound predicted values implies that for any day that cumulative exposure could occur, the drinking water component is at the high end. The Agency staff mentioned that, in addition to the 95th upper bound, it is also possible to model a statistically valid “highest” value. The Panel would be interested in reviewing such an exercise.

Modeling is a continuing process. It should always be validated and refined as data from monitoring programs become available. The Panel is encouraged that the USDA Pesticide Data Program (PDP) will include drinking water in the 2001-2002 list of commodities.

SESSION IV: INTEGRATED CUMULATIVE RISK ASSESSMENT

It has been very valuable to see the cumulative assessment model at this stage. The Agency is commended for making this integrated assessment, with all its current weaknesses, and putting the case study up for review. There is value to doing a modeling project even if all the information is not the best. The exercise itself raises the correct questions and issues.

In this case study, sources of exposure were identified for possible mitigation on the basis of their impact on the MOE at a given percentile. It should be noted that this method tends to pick out sources causing seasonal excursions. It doesn't readily identify sources that are high contributors to exposure but do not vary over the year. Policy will have to be developed for determining which sources of risk should be mitigated.

Use of assumed, fixed values for samples that are non-detects or <LOD leads to artificial suppression of variance in input variables and can negatively impact subsequent uncertainty analysis.

Question 10: The case study demonstrates the combination of data for food, water and residential exposures that reflect differences in the quantity of available data. Does the Panel have any concerns about combining data for different exposure sources that differ in the extent to which they describe anticipated real world exposures?

The uncertainty in the overall assessment is likely to be dependent on the quantity of the available data for each source, especially if the sources that have the largest proportional impact on the cumulative risk are also the sources that have the least reliable description of anticipated real world exposures. In these cases the tendency to grossly underestimate or overestimate the cumulative risk will be maximized. It is probably here that attention should be focused on obtaining the type of data necessary to develop reasonable estimates of cumulative risk. For exposure pathways considered to be minor, but which also suffer from deficit in the quantity of available data, the uncertainty will be related to the possibility that additional data might show a bias in previous estimates of the magnitude of exposure from this source. In this case a form of sensitivity analysis should be attempted to determine potential areas in which additional data would improve exposure estimates.

It is inevitable that dissimilar data will be combined in an aggregate and cumulative analysis. This should be dealt with through propagation of uncertainty. That requires that uncertainty and variability be distinguished. A 99.9 percentile from a 1-D analysis is much less defensible than an UCL of a lower percentile from a 2-D analysis.

The model cannot be fully evaluated without knowledge of its intended use. Both Agency personnel and others have suggested that pathways currently left out can be added later. Some risk exists that an expression of approval for the current version will create "facts on the ground" that could subsequently impede iterative improvement.

The model cannot be fully evaluated without real world (biomonitoring) data for comparison and that comparison cannot be made without 2-D representation of outputs. Biomonitoring data are highly recommended since it will enhance the credibility of the risk assessment.

There are concerns about combining data from different sources, especially when there are LOD differences. Detected values may be swamped by LOD data in another part of the model.

Also there are concerns about combining data with quite differing levels of precision and conservativeness, and about the use of one set of data to drive other model considerations. For example, if the water data examined is only for those OPs that show up as important in food, some OP or OP breakdown product important only in water or in dermal exposure may be overlooked.

Groundwater should be part of the big picture. Although it is probably not a major source in the case of OPs, it may be a significant contributor to the risk picture with some other pesticides. The current model uses stream and reservoir water prior to the water plant. In some areas, waters are mixed so that surface and ground water both may be used. Using raw water may be more conservative than using treated water, but this may not always be the case.
The issue of differences in quality of data used in the cumulative risk assessment will only be resolved by further data collection to assure that the quality of data used in future assessments is consistent. In the meantime, the Agency should continue with this effort using the data presently available.

One concern is why, for pesticides C, T, and P used in crack and crevice applications, only inhalation exposure was considered. This is a concern particularly considering that the model assumes that pesticide C remains for 3 days unchanged in air concentration, and that T and P had active exposure periods of 30 days. This would appear to be a very dynamic environment. It would seem that this is not making the best use of the data the Agency has. In addition the lack of inclusion of other routes of exposure biases the result toward inhalation. Several models presented at ISEA which took into account other routes of exposure suggest that dermal and non-dietary routes of ingestion may play important roles for children.

Question 11: In the current integrated case study, the contribution of water relative to other sources of exposure is very small. This pattern was evident from the initial single source assessment that preceded the integrated cumulative assessment. This approach could be used as a form of sensitivity analysis to simplify of the overall assessment. Can the Panel recommend any considerations in determining the extent to which minor contributors to risk can be eliminated from an integrated cumulative risk assessment? Generically, can the Panel identify any major concerns or pitfalls in this approach?

The contribution of water to cumulative exposure needs to be considered on a regional (or even smaller geographic unit) basis. What may be a minor contribution in one setting may not be minor in another.

It may be necessary to develop geo-regions for different components of exposure. For example, it may be cost-effective to develop the water model for a large region but use smaller regions for residential exposure (due to pest pressures) or diet (due to ethnicity differences). The final analysis would then be run for smaller regions created as the interception of these regions. This way, data from larger areas can be used effectively to address the smaller regional analysis.

EPA, perhaps quite naturally, would like to simplify the problem at hand by eliminating elements that have only a negligible contribution to the cumulative exposure and its resulting risk. The Panel has some sympathy for the desire to lighten the analytical burden. However, as many members of the Panel have remarked, one cannot conclude a value is virtually zero if its magnitude has not been assessed.

The Panel was concerned that several contributors to exposure were ignored as a way to lighten the analytical burden. The sum of minor contributors can, in some circumstances, be as large or larger than any major contributor. In environmental science, this phenomenon is sometimes called the "death of a thousand cuts". The point of doing a *cumulative* assessment is to assess the possibility of "a death of a thousand cuts" in which many individually small exposures result in a toxicologically significant exposure. In general, analysts cannot tell in advance of doing a comprehensive analysis whether any contribution will end up constituting a negligible portion of the whole, so the advantage of leaving contributors out of the assessment may really be illusory in practice.

There are, however, two strategies that could be used to lighten the Agency's analytical burden. The first is to narrow the population of interest. For instance, it might be advantageous to restrict the question in terms of population exposed. Analysts have made use of this strategy already by focusing on two narrowly defined populations of children and adults in the Piedmont region. The second strategy is to use intervals rather than point estimates in the Monte Carlo simulations. Even when analysts cannot obtain good estimates, it is often possible to obtain sure bounds on quantities. If the upper bound is very small, then the contribution is surely tiny, even if the bounds are relatively wide and span many orders of magnitude. These intervals can be used in a Monte Carlo simulation in a straightforward way. This approach simplifies the problem by significantly reducing the burden of data collection and parameterization. This approach is also computationally simpler than second-order Monte Carlo simulations and still distinguishes variability and uncertainty (i.e., incertitude or ignorance). Using intervals in a Monte Carlo simulation avoids creating a mix of partially probabilistic and partially deterministic estimates.

Exposure and risk assessments that appear to represent obvious conclusions can be dangerously misleading if they ignore uncertainty and make no assessment of their own reliability. Conclusions that initially appear quite clear, for instance that some route of exposure is negligible, may be very misleading if the uncertainty about the estimate is very large. A Monte Carlo assessment that uses intervals to bound incertitude can detect when such uncertainty is large.

As a starting point, if, using simple deterministic models with conservative assumptions risks from all routes are relatively small and water is a small percentage of this calculated risk, then there is little need for developing full probability distributions. But you don't know how small the contribution is unless you do the calculations, and what is true for OPs may not be true for other compounds.

The amount of effort should be adjusted as a function of the percentage of the overall exposure from the water pathway: if the deterministic conservative worst case exposure is very small relative to the other routes, then the assessment should not be more complicated than necessary. Resources should be spent on providing the best estimate of exposures by the other routes. The caveat to this is that this doesn't mean throwing out water (e.g., in all cases) since it's magnitude may change if carbamates are added or for other pesticide families with the common mechanism of action.

It is important to leave everything in the case study until a reality check can be conducted. The water pathway approach used in the case study seemed to receive (lukewarm) approval primarily because it is probably unimportant for OPs. This is unlikely to be true in other cases. Whether we are being asked to comment on a general approach rather than a specific case makes a difference.

Question 12: The cumulative assessment in the case study was limited in geographic scale to the Piedmont areas of Virginia, North Carolina, and South Carolina in an attempt to focus the scale of the assessment on an area of consistent seasonal variation and pest pressure. In this way, OPP hopes to develop an integrated assessment within which the water and residential uses are relative constant, making the risk assessment relevant for that particular area and other areas like it. Does the Panel find the geographic scale to be appropriately limited such that the results of the risk assessment are applicable across the entire area? What considerations should OPP apply to define the appropriate geographic scale for drinking water and residential cumulative risk assessments? Does the Panel see major pitfalls to this approach?

The small geographic unit used in the model was excellent, well thought out, and appropriate. Trying to define what is an appropriate geographic unit for other areas of the country may be challenging given the paucity of usage data. However, the criteria used in this case are valuable: climate, common pest pressures both indoors and outside, and some measurement of pesticides in water specific to that area. Both dietary and activity pattern factors may be regionally or culturally specific. Some effort may be needed to include the variations in these factors. Climate will also drive seasonal use of pesticides and activity patterns.

For residential exposure, it is appropriate to try to define the geographic unit of analysis in terms of similar pest pressure. It is reasonable to think that residential use practices will be relatively homogeneous within a region having common pests, although there will be differences according to dwelling type and urban/suburban/rural location, and these should be addressed in the exposure simulation. Climatic data are appropriately used to identify regions of similar pest pressure.

Defining the right scale for drinking water is more difficult. In principle, the correct unit would seem to be the CWS, but it is not feasible to do an assessment for every water supply. It could be productive to pursue modeling to relate concentrations at water intakes to use for representative types of watersheds.

Large ethnic minorities within a region that might have significantly different food consumption from the general population should be examined.

The scale of assessment is probably about right. It needs to balance the need for sufficient variation to develop reasonable estimates of distributions, while also having sufficient commonality in pesticide usage (pest pressure, cropping systems, etc), climate, diet, and land resource features to result in common exposure potential. Attention should be paid to potential anomalies (e.g., ethnic subpopulations).

Question 13: The data used in single chemical assessments often contains many sources of overestimation bias. However, because the cumulative risk assessment is developed from combining data from many sources and describing many pesticides, concerns for compounding conservatism is greater than for single chemical assessments. In the current case study, OPP has taken the approach of depending to the extent possible on monitoring data which most closely approximates real world exposures and has applied the value of zero where no detectable residues were available for food residues. Are these conventions reasonable given the complexities and uncertainties inherent in combining many data sets to develop an integrated, multi-chemical, multi-pathway risk assessment?

The case study presented a framework for combining the risks from multiple routes and multiple chemical exposures. The case study showed how a component may be included or excluded and how these choices would affect the outcome of the cumulative risk estimates. In addition, the case study identified some key data gaps and illustrated how decisions could be made for bridging these gaps. The overall goal is to ensure that the assessment does not overly overestimate the risk and yet is conservative so as to not underestimate the risk.

The general goal of staying on the conservative side but not overly overestimate the risk is a reasonable one. The preference for using representative monitoring data of good quality is also a valid one, although this is a luxury that residential and drinking water components often do not have.

The case study demonstrated the thought process behind choosing to use surrogate data versus not addressing a component of exposure due to lack of data. The choice of zero concentrations when no detectable residues were available for food residues is a more difficult assumption to obtain consensus on. The professional judgement and rationale behind this assumption needs to be clearly articulated.

The case study is also useful for illustrating some options for characterizing the possibility of co-existence of multiple pathway and multiple chemical exposures. These included extrapolating from similar data assuming co-existence in a simple additive way. In general the decision process as presented in the case study is reasonable. The Panel has also recommended several areas for future consideration.

Lastly, the case study represents the first attempt to carry out the concept of cumulative risk assessment approach. As such, the Agency's approach in using this case study to demonstrate some impacts of the various choices of approaches is very much appreciated. Invariably, the decision process becomes easier when the impact of these choices (e.g., whether to include an exposure component) can be illustrated. However, caution should be given in drawing conclusions based on the comparative contribution of pathways of exposure. Such comparison requires the considerations of both the exposure and the toxicological data. The case study demonstrated several important points regarding the toxicological considerations:

1) The importance of choosing the index chemical in the relative potency factor (RPF) approach. There was nearly one order of magnitude difference between the two options for the point of departure (PoD) for the dietary pathway; the ED_{10}, and the NOEL. Thus, using one PoD over the other significantly affected the relative pathway contribution to the overall exposures (i.e., comparing Appendixes A and B in the case study). The wide difference in the ED_{10} and the NOEL may mean that there was a wide distance between the acute NOEL and the LOEL for the index chemical. With the richness of the oral toxicity database for OPs, the tightness between the ED10 and NOEL could be considered in choosing an index chemical such that the uncertainties in the toxicity side of the risk equation could be minimized. Once an index chemical is selected, it may also be possible to obtain better data for the index chemical.

2) While a comparison between ED_{10} and the NOEL was possible for the oral route, a similar comparison was not possible for other routes of exposure. The disparity in the richness of the available data further adds to the uncertainties in the pathway-specific comparison of contribution.

3) Route-specific uncertainties in toxicity data also contribute to the difficulties in drawing conclusions on the relative pathway contributions. While calculating cumulative MOE based on route-specific MOE would reduced the uncertainties of route-to-route extrapolations, route-specific uncertainties remain. As a result, the MOE of 100 from one pathway is likely to have different meaning than the MOE of 100 from another pathway. Thus, these uncertainties would

have to be carefully weighted in the comparative pathway-specific contribution analysis.

It is not reasonable to use a value of zero whenever residues were not detected. Some members of the Panel consider this an ethical issue. It is entirely reasonable for an analyst to use modeling or structural knowledge derived from intended use or market share data to conclude that certain residues are likely to be zero. But a blanket policy of replacing non-detects with zeros is an abdication of an important responsibility of the analyst. Suggesting that this policy depends to the extent possible on monitoring data which most closely approximates real world exposures may make the practice sound legitimate, but the justification is specious. Analysts should not hide behind the data merely to avoid doing the admittedly tedious work of explicating their presumptions about which concentrations should be treated as zeros. They need, in short, to *say why* a value is set to zero. Non-detects from the laboratory should then be considered corroboration of their explanations. This issue is not simply a question of conservativism. Using zeros does not automatically make an assessment more realistic. It is a question of the reliability of the final estimates and the prudence of using these estimates in regulatory practice.

In the description of the model, (p.13, 2) it says that occasionally, for various reasons, there are no entries for some pesticides on some samples. In such instances, it was assumed that those pesticides with no entries had zero residues. This makes sense only if one knows what are the various reasons. In some cases no entry means missing data and should not be interpreted as zero.

The convention of ascribing zero to foods with no detectable residues may be reasonable when the limit of detection is very low and there are few samples with non detects and if the limits of detection are similar for all the pesticides used in the cumulative risk assessment. If the limits of detection for the pesticides are highly variable, setting non detects to zero should not be done. In the figure of grape analysis there was an order of magnitude difference in detection levels. It is unclear how non-detects would be treated in this case.

If this convention is to be used, it must be justified. If used for food, should it also be used for water samples, dust samples, and air samples? If not, how does OPP justify the usage with one set of measures but not with others?

Close distributional approximation to real world systems should be the basis for simulating cumulative exposures and risks. Ideally, the inputs from each source and pathway should reflect stochastic variability that is representative of the real world.

Why conservatism? If conservatism is intended to provide a margin of protection, wait until the full stochastic assessment is complete and add the margin. If conservatism is intended to account for extreme events that occur rarely in the population, it is better to model the extreme events at appropriate levels and frequency. Where ranges of values and distributional forms are not well known, conservative assumptions should be applied but again in the context of reasonable distributions over populations and time. For residues below the LOD, the stochastic distribution employed should include data on percent of crop treated (structural zeros) and a reasonable distribution for the tail on the non-zero residues that lies below the LOD censoring point. Specifications and assumptions for each input should be clearly identified in the output documentation. As the context of the model changes (e.g. new residential data, new compounds), sensitivity analyses should be repeated to test the effect of simplifying assumptions.

The conservatism or lack thereof in the integrated, multi-chemical, multi-pathway risk assessment is influenced not only in the accurate representation of real world distributions in the single chemical, single mechanism pathways but also the associations between compounds and pathways. Co-occurrence of residues in source exposures and correlation in concentrations are important to accurate simulations. If correlation in co-occurring compounds for sources (foods, water, residential uses) is positive, independent evaluation of pathways for each chemical will shrink both tails of the exposure distribution. If correlations are negative, the opposite effect will occur.

REFERENCES

Cullen, A. and Frey, H.C. 1999. Probabilistic techniques in exposures assessment: A handbook for dealing with variability and uncertainty in models and inputs. Plenum Press.

Edwards, R.D.and Lioy, P.J. 1999. The EL sampler: a press sampler for the quantitative estimation of dermal exposure to pesticides in housedust; J. Expo. Anal. Environ. Epidemiol., 9, 521-9.

Millstein, J.A. 1994. Propagation of measurement errors in pesticide application computations. *International Journal of Pest Management* 40: 159-165.

Millstein, J.A. 1995. Simulating extremes in pesticide misapplication from backpack sprayers. *International Journal of Pest Management* 41: 36-45.

Reed, K.J., Jimenez, M., Freeman, N.C., and Lioy, P.J. 1999. Quantification of children's hand and mouthing activities through a videotaping methodology; *J. Expo. Anal. Environ. Epidemiol.*, 9, 513-20.

Zartarian, V., Ferguson, A., and Leckie, J. 1997. Quantified dermal activity data from a four-child pilot field study. JEAEE 7(4):543-552.

Zartarian, V., Ferguson, A., and Leckie, J. 1998. Quantified mouthing activity data from a four-child pilot field study. JEAEE 8(4):543-553.