I. Revised OP Cumulative Risk Assessment

F. Cumulative Assessment

1. Introduction

The previous four sections of this document have described the development of the major components of the risk assessment. They describe a highly complex process of combining multiple data sets to develop a description of the possible risks from OP pesticides by each of the pathways described. OPP has had to develop new methods for each component of the assessment in order to produce an assessment which presents as realistically as possible the potential exposure to OP pesticides. The purpose of this section is to explain the concepts used to accumulate risk from each pathway into a total risk estimate, and to provide a basis for understanding the presentations that are provided in Section III for each of the regional assessments.

2. Basic Concepts

The definition of cumulative risk developed as a result of the passage of FQPA requires OPP to conduct a risk assessment for a group of pesticides with a common mechanism of toxicity that is multi-pathway, multi-route, and multi-chemical in scope. As described in section I.B above, the RPF method was used to address the issue of combining toxic responses from OPs with varying propensities to inhibit acetylcholinesterase. Exposure to each OP was normalized to equivalent exposure to the index compound, methamidophos. The toxicity data currently available for conducting this analysis are estimates of response by route-specific dosing, and do not support estimating delivered dose to the target tissue. OPP decided to address this problem by comparing route-specific exposures to route-specific points of departure to produce unitless margins of exposure for each route. In this case, the POD was a BMD_{10}. MOEs were combined by taking the inverse for each route, adding them together, and then taking the inverse of that sum. This process was used to produce a distribution of daily estimates for the subpopulation of concern that reflects regional and seasonal variation in the patterns of exposure that are likely to occur throughout the US across the year. OPP used a probabilistic assessment to capture the full range of exposure possibilities from all sources analyzed. The intent was to produce an estimated range of risk that is as realistic as possible. The OP cumulative risk assessment is not a high end risk assessment. It attempts to reflect the full range of likely exposures for consideration in a regulatory context. However, at the same time it is designed to avoid developing extreme exposure estimates based upon the combination of exposure scenarios and assumptions that are not reasonable.

3. Framing the Population-Based Assessment

OPP focuses its risk assessment on exposure and resulting risk to the population, not to risk to an individual. This distinction is an important one with regard to defining how the components of the assessment will be combined. The current assessment focuses on highlighting inter-individual patterns of exposure instead of attempting to define intra-individual patterns of exposure. OPP made this choice because of the lack of acceptable longitudinal data defining intra-individual behavior for any component of the risk assessment. This issue has been repeatedly discussed at SAP meetings reviewing the conduct of dietary risk assessment methodology. Longitudinal data permitting modeling of the consumption of food and water by the US population is not available. The data describing the use of pesticides in a residential setting is even more uncertain. Although ranges of use parameters are available and have been used in this assessment, they are only adequate to define the behavior of the population across time, and cannot accurately reflect the day to day variability in behavior of an individual. Therefore, OPP decided to develop a series of daily exposure distributions and array them as a distribution across time.

The distribution of daily exposures and resulting MOEs are developed such that the exposures from OPs in foods, drinking water, and from residential uses are all calculated simultaneously for each hypothetical individual in the subpopulation. OPP uses the Calendex software to develop the distributions and resulting MOEs. Calendex permits incorporation of time course information with regard to residential uses of pesticides, but does not permit specific allowance for regional variability. OPP addressed this issue by running separate risk assessments for each of seven regions of the US. The regions correspond to agronomic cropping areas and reflect climatic and soil conditions that are likely to affect pest pressure and resulting pesticide use. Regional differences in pesticide use are major considerations in appropriately estimating exposure from pesticides in drinking water and residential uses.

To generate a daily distribution of exposure, consumption records are selected from the CSFII for each individual in the survey. Calendex uses this consumption record to estimate OP exposure from food by randomly assigning a residue value for each food reported consumed by that individual. After multiplying each amount of food consumed by its selected residue value, the total exposure from food for this individual is calculated by summing the exposures from the individual foods which were reported consumed. At the same time, all appropriate residential scenarios that may be encountered for the calendar day 1 (January 1) are reviewed. A probability-based decision is made as to whether or not that scenario will be encountered (e.g., a lawn treatment would probably not occur in January in the Northeast/North Central region). If the scenario is assigned a "yes" answer (i.e., treatment does occur), then the appropriate values defining the exposure are selected from the many distributions of input parameters for residential exposure scenarios. The exposures for the dermal, oral and inhalation pathways are calculated for all

selected residential scenarios. A drinking water value taken from the PRZM/EXAMS output for January 1 is selected and paired with the water consumption reported in the CSFII consumption record. These values are used to calculated exposure from drinking water for that date. All of the exposures are converted to route-specific MOEs to define the total exposure to the hypothetical individual on January 1. The process is repeated for each consumption record for the age group in the CSFII ten times (i.e., ten iterations) to build a distribution of exposures for January 1. This process is repeated for January 2, January 3 and so forth across the year.

The 365 daily exposure distributions are arrayed together in order to provide a profile of possible exposures by each route and in total as MOEs. An example of such a distribution of distributions is presented in Figure I.F.1. In this figure, each daily distribution is arrayed on the yz plane of the plot. Day 365 can be clearly seen on the right side of the plot. This distribution of total risk is expressed as a cumulative distribution function of MOEs versus percentile of exposure. Percentile of exposure refers to that portion of the population output distribution that has less than or equal exposure. For example, at the 80^{th} percentile of exposure, 20% of the output distribution has an MOE lower than the one at the 80^{th} percentile point on the distribution.

The distribution of daily distributions is used to estimate the potential risk, with accompanying distributions generated for each pathway and route. OPP acknowledges that this approach does not describe intra-individual risk. In all likelihood, the variability in an individual exposure would be much greater than in a population-based approach because of the limited likelihood of repetitive events such as residential pesticide applications. However, the population at large will experience some degree of exposure each day. This factor is a likely source of conservatism in the current assessment.

4. Interpreting the Outputs

The results of the final assessment are presented in tabular (Calendex output) form in the appendices. The reflect year-long slices across the 3-dimensional plot in Figure I.F.1. In that plot, dark lines can be seen across the total MOE surface. For instance, the top line in the 3-dimensional plot represents the 99.9^{th} percentile of exposure for the population. A slice through the surface parallel to the xy plane at the 99.9^{th} percentile would look like the plot presented in Figure I.F.2. This plot presents the potential total MOE for the exposure scenarios included in this assessment. In addition, the contributions from various pathways and routes of exposure are arrayed separately to assist the risk manager in identifying contributors to risk for further evaluation. Other age groups (or percentiles) of exposure may also be of interest. For example, Figure I.F.3 presents the results of the 99.9 percentile assessment for the age group Adults, 20-49.

5. The Rolling Time Frame Approach

One important aspect of the revised cumulative risk assessment for the organophosphate pesticides (OPs) is the manner in which estimated exposure is compared with toxicity endpoints. The above paragraphs detail and describe one "mode" or option of analysis (termed the *single consecutive day* option) in which separate, independent estimates are made for each day of the year (January 1, January 2, etc.). As discussed above, these can be arrayed into an exposure timeline for any selected percentile (and graphed, if desired). That is, for example, the estimated 99.9th (or any other percentile) percentile exposure value is calculated by DEEM/Calendex for each day of the year from January 1 through December 31. These represent independent daily estimates of the 99th percentile exposures on each day of the year and do not necessarily represent the same individual on consecutive days[1]. Thus, it is NOT possible (with this mode of analysis) to interpret an extended period (or series) of elevated exposures over time as necessarily representing extended exposures to the *same* individual, and comparison of any estimated exposure to multi-day endpoints (e.g., a multi-day BMD_{10} would be expected to provide a very conservative estimate of risk to the extent that exposures on consecutive days at any given percentile are unlikely to be the same individual.

[1] For example, biomonitoring data from CDC and others indicate that a sizeable percentage of the U. S. population has measurable levels of OP metabolites in their urine or blood.

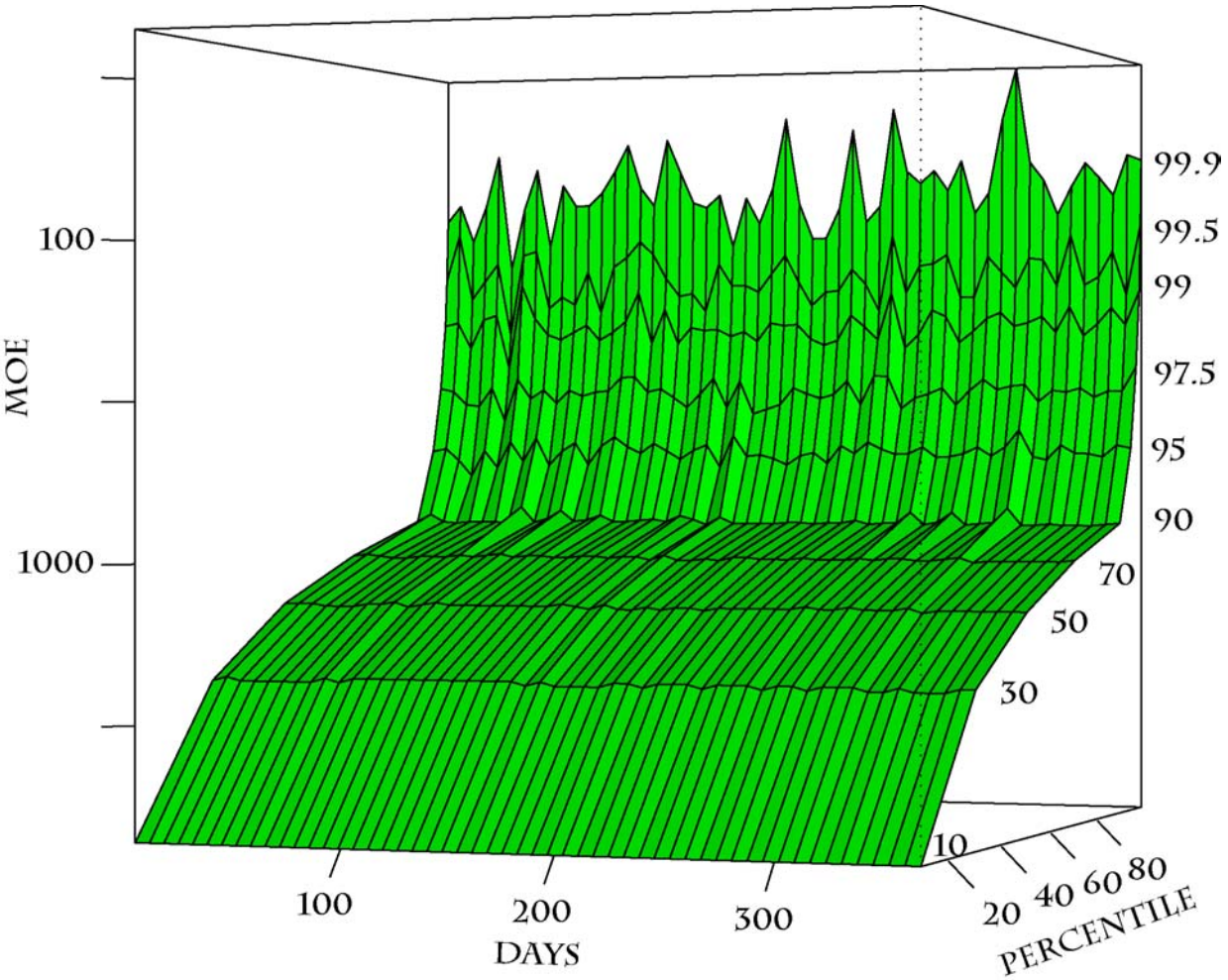


Figure I.F-1. Three-dimensional plot of the total MOE by day of the year and percentile of exposure

Figure I.F-2. Cumulative Assessment - 99.9th Percentile Estimate for Children Ages 1-2 Years for All Routes and Pathways

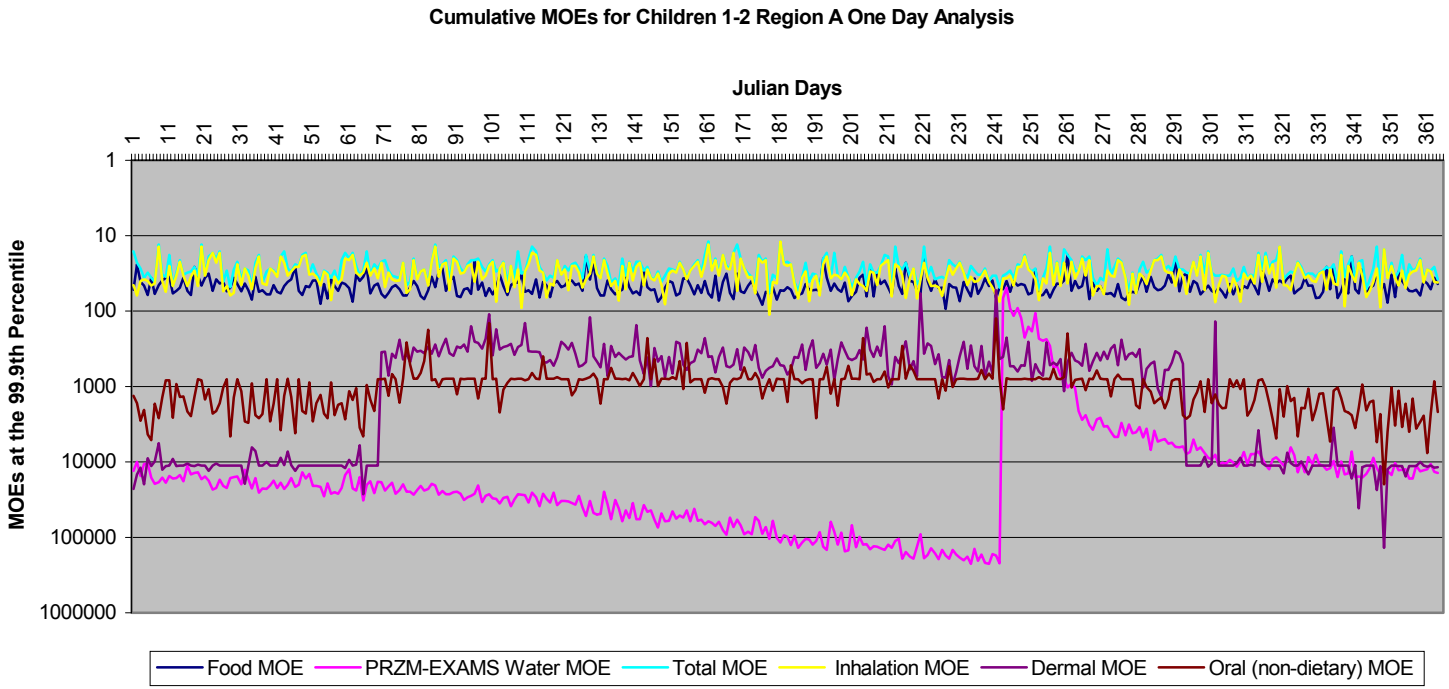
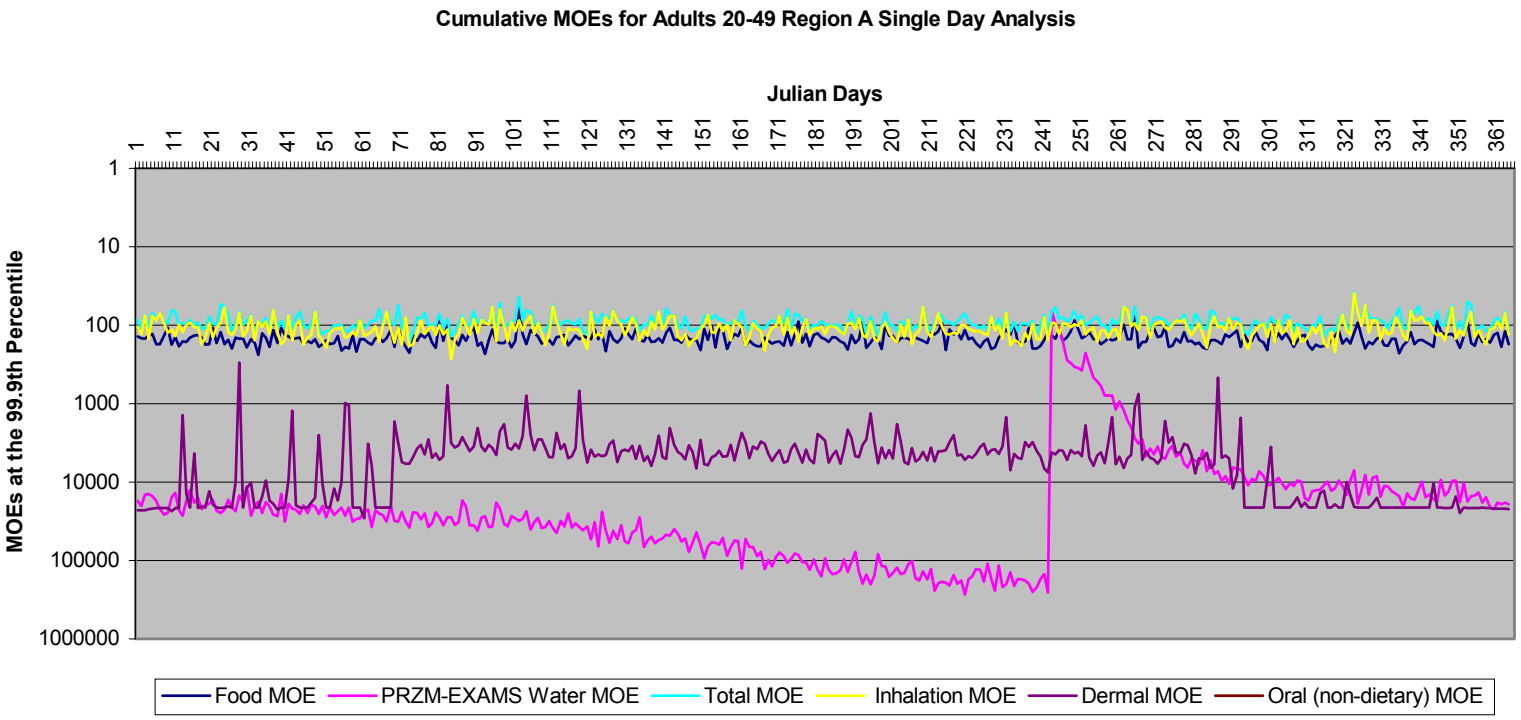


Figure I.F-3. Cumulative Assessment - 99.9th Percentile Estimate for Adults 20-49 Years for All Routes and Pathways



The DEEM/Calendex program can perform analyses under a second option. Under this second option (termed the *multiple sequential day option*), a rolling (or sliding) time frame is used and multi-day average exposures are calculated for each individual (e.g, average exposures for each individual for January 1 through January 7, January 2 through January 8, etc.). Under this mode, average exposures over multiple consecutive days (e.g., January 1 through 7, January 2 through 8, etc.) are assessed for the same individual. It is then this distribution of multi-day average exposures at any given percentile which serves as a basis of comparison with the (multi-day) BMD_{10}. An example graph of this is presented in Figure I.F-4 which shows a seven day rolling average exposure profile for Children 1-2.

In the Preliminary Cumulative Risk Assessment, exposures were estimated on a single-day basis (the first option) and a comparison made of each independent DEEM-estimated single-day exposure with the steady-state (21 day) equilibrium BMD_{10} value That is, separate exposure estimates were made for January 1, January 2, etc. for each individual in the CSFII survey *for each (single) day of the year* with exposure at a given percentile (e.g., 99^{th}) calculated and compared to a multi-day BMD_{10}. In viewing these results, and despite their one-day exposure basis, OPP is NOT concerned with exposure spikes lasting only one or perhaps a few days since the MOE's associated with these "spikes" are based on multi-day toxicity endpoints. Rather, OPP is interested in extended periods of high exposure (or, equivalently, low MOEs) which indicate not that an *individual* is being exposed to high levels of OP pesticides over a multi-day time period, but instead that the overall level of exposure to the sub-population in the tails of the distribution has increased. This is an important distinction which brings up two issues:

- ❏ comparing a series of elevated single-day exposures to multi-day endpoint may have less relevance than comparing a multi-day average exposure (at any given percentile) to a multi-day endpoint.

- ❏ Consecutive single-day estimates of exposure are likely to significantly overestimate multi-day exposures to an individual (at higher percentiles) e.g., the 99.9th percentile individuals are unlikely to be the same individual on consecutive days.

An alternative option – which was explored and incorporated into this revised CRA and supplements the *single consecutive day option* – is to estimate multi-day rolling average exposures in which average exposures over multiple consecutive days (e.g., January 1 through 7, January 2 through 8, etc.) are assessed for the same individual. It is this multi-day average exposure which then serves as a basis of comparison with the (multi-day) BMD_{10}. There are a number of advantages to this alternative. In addition to providing a means of estimating exposure which is more directly comparable to a multi-day endpoint, the multiple sequential day mode of analysis better incorporates variability in exposure for an individual across multiple days and is likely to provide a more

realistic estimate of exposures for individuals across multiple days. It is also flexible with respect to matching time-frame associated with BMD10 in that multi-day averages can be calculated over 7, 14, 21, or 28 days. However, as discussed in the February 2002 Scientific Advisory Panel meeting associated cholinesterase inhibition level will be underestimated if one fails to allow for the residual (or lingering) cholinesterase inhibition effect from those previous days in cases where a day's exposure is preceded by nonnegligible exposures on previous days.

Figure I.F-4. Cumulative Assessment - Seven Day Rolling Average 99.9th Percentile Estimate for Children Ages 1-2 Years for All Routes and Pathways