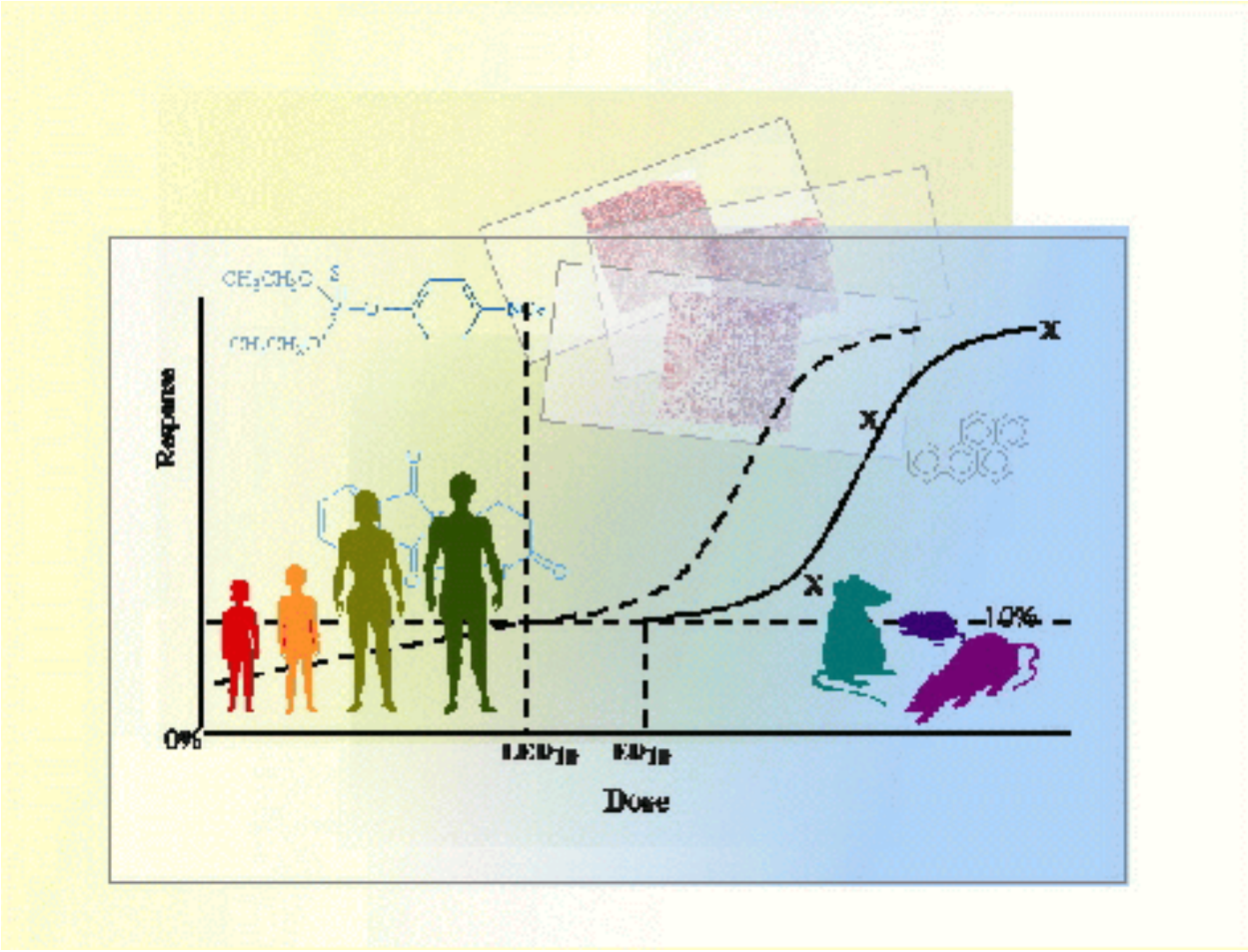
Organophosphorus Cumulative Risk Assessment

2006 Update



U.S. Environmental Protection Agency
Office of Pesticide Programs

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Organophosphorus Cumulative Risk Assessment -- 2006 Update

Technical Executive Summary

As mandated by the Food Quality Protection Act (FQPA,1996), EPA must review by August 3, 2006 the safety of all existing tolerances (maximum residue allowed on a food) that were in effect as of August 1996. The law requires EPA to place the highest priority for tolerance reassessment on pesticides that appear to pose the greatest risk, including the organophosphorus pesticide (OP) class of pesticides. Over the last several years, the Office of Pesticide Programs (OPP) has been conducting risk assessments for individual OP pesticides and, where necessary, has implemented mitigation measures to reduce exposure to these pesticides.

As part of this process, EPA must consider available information concerning the cumulative effects on human health resulting from exposure to multiple chemicals that have a common mechanism of toxicity. A cumulative risk assessment incorporates exposure data from multiple pathways (i.e., food, drinking water, and residential/non-occupational exposure to pesticides in air, or on soil, grass, and indoor surfaces) for those chemicals with a common mechanism of toxicity. EPA began developing new tools and methods for conducting cumulative risk assessments on pesticide chemicals shortly after the enactment of FQPA and has conducted various iterations of a cumulative assessment for the OP pesticides beginning in 2001 with the Preliminary Organophosphorous Cumulative Assessment[1].

In June 2002, the EPA released its Revised OP Cumulative Risk Assessment (OP CRA), which included the cumulative risk due to the OPs from exposures in food, drinking water, and residential uses. The revised OP CRA document is available at http://www.epa.gov/pesticides/cumulative/rra-op/. The current (2006) document is an update to this 2002 revised version and emphasizes changes, modifications, and amendments to the 2002 Revised OP CRA. The current update incorporates risk mitigation taken by the Agency which impact food, drinking water, and/or residential risk estimates. Key additions to the hazard and dose-response assessment include evaluation of inter- and intra-species extrapolation and assignment of OP-specific FQPA factors for the

[1] This document is located at http://www.epa.gov/pesticides/cumulative/pra_op_methods.htm

protection of infants and children. In the food exposure chapter, the Agency has extended pesticide residue data in food to include USDA's Pesticide Data Program (PDP) data through 2004. The Agency has also considered the extent to which conversion of OPs to oxon metabolites as a result of drinking water treatment could impact risk. This document includes a brief introduction which highlights some of the activities of the Agency since the release of the 2002 Revised OP CRA document and major differences between that 2002 document and this update; summaries of the detailed technical issues and methods associated with conducting of a cumulative risk assessment; presentation of exposure and risk results from food, water, residential, and multi-pathway assessments; and a comprehensive characterization of the overall cumulative risk. The reader is referred to the 2002 revised CRA for a more complete description of technical methods and approaches.

The methodology used in this 2006 Update is the same as was presented in the previous 2002 document. These methods have been reviewed by the FIFRA Scientific Advisory Panel (SAP) numerous times in the past, resulting in well-documented, transparent, and scientifically supportable methods for assessing the risk of exposure to multiple OP pesticides and for evaluating the range of population exposures that might be expected. EPA has relied on the FIFRA SAP to peer-review guidance documents, methods, approaches, and pilot analyses to ensure that EPA is using appropriate methods and sound science. In addition to the SAP reviews, EPA has sought and considered public comments on these approaches as it developed these cumulative assessment methods.

A cumulative risk assessment begins with the identification of a group of chemicals, called a common mechanism group, that induce a common toxic effect by a common mechanism of toxicity. Pesticides are determined to have a "common mechanism of toxicity" if they act the same way in the body--that is, the same toxic effect occurs in the same organ or tissue by essentially the same sequence of major biochemical events. The OPs were established as the first common mechanism group by EPA in 1999 (USEPA, 1999). OPs share the ability to bind to and phosphorylate the enzyme acetylcholinesterase in both the central (brain) and peripheral nervous systems. When acetylcholinesterase is inhibited, acetylcholine accumulates and cholinergic toxicity results due to continuous stimulation of cholinergic receptors throughout the central and peripheral nervous systems which innervate virtually every organ in the body.

Once a common mechanism group is identified, it is important to determine what chemicals from that group should be included in the quantification of cumulative risk. In choosing the specific OP pesticides to be included in the cumulative risk assessment, EPA considered risk mitigation decisions and exposure potential. EPA identified three exposure pathways of interest: food, drinking water, and residential/ non-occupational for these pesticides. Each of these pathways was initially evaluated separately, and, in doing this step of the analysis, EPA determined which of the OPs were appropriately included for a particular pathway. The cumulative assessment of

potential exposure to OPs in food includes OP pesticides that are currently registered in the U.S. or have import tolerances. The drinking water exposure pathway includes OP pesticides with registered uses in the U.S. that can potentially reach water bodies (i.e., outdoor uses). The earlier OP assessments of the residential exposure pathway considered 8 OPs (acephate, bensulide, DDVP, disulfoton, malathion, naled, TETRACHLORVINPHOS, and trichlorfon) registered in the U.S. for home use. The current assessment reflects the most up-to-date or best available residential use picture for these chemicals.

There are many steps involved in quantitatively assessing the potential human risk associated with the OP pesticides. The complex series of evaluations involved hazard and dose-response analyses; assessments of food, drinking water, residential/non-occupational, and cumulative exposures; and risk characterization. These steps are described more fully in OPP's Cumulative Guidance (US EPA, 2002a) and the 2002 Revised OP Cumulative Risk Assessment. The approach to each of these components and their results is briefly explained below:

- ❑ Selection of an index chemical to use as the point of reference to standardize the toxic potencies of each OP, determination of the relative toxic contribution of each OP, and establishment of a value to estimate potential risk for the group;
- ❑ Evaluation of inter- and intra-species extrapolation and variability along with consideration of potential sensitivity to infants and children;
- ❑ Estimation of the risks associated with all pertinent pathways of exposure (i.e., food, drinking water, residential) in a manner that is both realistic and reflective of variability due to differences in location, time and demographic characteristics of exposed groups;
- ❑ Identification of the significant contributors to risk; and
- ❑ Characterization of the confidence in the results and the uncertainties encountered in the assessment.

Hazard and Dose-Response Assessment:

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

the toxic potencies and calculating relative potency factors for each OP pesticide. Toxic potencies for the OPs were determined using brain cholinesterase inhibition from female rats measured at 21 days of exposure or longer. Following approximately 3-4 weeks of exposure to OPs, cholinesterase inhibition is no longer increasing following OP exposure. This point where cholinesterase inhibition at a given dose is fairly constant is called steady-state. In the Preliminary CRA for the OPs, the Agency showed that estimates of potency are reliable and reproducible when estimated at steady state. Brain cholinesterase inhibition is a direct measure of the mechanism of toxicity, and thus does not have the uncertainty associated with using blood measurements of cholinesterase inhibition which serve as surrogates for cholinesterase inhibition in the peripheral nervous system. Furthermore, relative toxic potencies derived from brain data were shown in the preliminary assessment to be generally similar to those derived from red blood cell data and showed less variability, and thus less uncertainty.

The Agency used an exponential dose response model to develop benchmark dose estimates at a level estimated to result in 10% female brain cholinesterase inhibition (i.e. BMD_{10}) to estimate relative potency for the oral route and to develop points of departure (PoD) from the oral, dermal, and inhalation routes for methamidophos, the index chemical. A PoD is a point estimate on the index chemical's dose-response curve from which risks associated with the exposure levels anticipated in the human population are extrapolated. EPA compares estimated exposures with the PoD value to calculate Margins of Exposure (MOE) and to estimate potential risk to humans.

In order to assign the appropriate FQPA 10X safety factor for the protection of infants and children, a screening-level approach was used to identify a subset of OPs considered to be potential contributors to the cumulative risk either from food, water, or residential pathways. Following this screening approach, the Agency searched the scientific literature and pesticide registration databases for toxicity studies which measured brain ChE inhibition in juvenile and adult rats following repeated dosing. The Agency's refined FQPA safety factor analysis focused on 13 OPs[2] which were identified during the screening approach and which had a repeated dosing, comparative ChE study. For all other OPs, a FQPA factor of 10X was retained. In the refined FQPA safety factor analysis, the Agency used benchmark dose techniques and/or plots of data from juvenile and adult rats to evaluate potential age related sensitivity.

Since each OP has been assigned its own FQPA safety factor, the Agency has mathematically applied the value of the FQPA safety factor directly to the RPF for each OP. In addition, the Agency has used the standard 10X factors for inter- and intra-species extrapolation for all the OPs. Thus, to account for the inter- and intra-species extrapolation, the target MOE for OP CRA is 100.

[2] The results of the analysis for dimethoate have been applied to direct exposures to omethoate, the oxon metabolite of dimethoate.

Exposure Assessment:

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

All of the hazard data, exposure data, and exposure scenarios must be combined in a manner designed to produce reasonable and realistic estimates of exposures likely to be encountered by the public in location and time (seasonally). As was done in the 2002 Revised OP assessment, EPA used Calendex™ software to integrate various pathways while simultaneously incorporating the time dimensions of the data[3]. Calendex™ provides a focused, detailed profile of potential exposures to individuals across a calendar year.

Exposures through residential uses and in drinking water are incorporated into cumulative exposure assessments on a regional basis. EPA conducted seven high potential exposure regional assessments for drinking water and joined these with generic residential exposure scenarios generally representative of regions in the Southern US. These regional assessments are meant to account for differing agronomic uses and reflect the differences in climate, soil conditions, and pest pressures across the entire US. Exposures that are represented in these generic residential exposure scenarios are not expected to be exceeded in any region in the US. Exposure to OP pesticide residues in foods is considered to be uniform across the nation (i.e., there are no significant differences in food exposure due to time of year or geographic location). The assumption of nationally uniform food exposure is based on the understanding that, to a large extent, food is distributed nationally and food consumption is independent of geographic region and season. The single national estimate of food exposure was combined with region-specific exposures from residential uses and drinking water in three regions that represent the highest potential for exposure.

In previous versions of the OP CRA (2001, 2002) the Agency presented exposures and risks associated with exposure durations of a single day and of rolling averages ranging from 7 to 21 days in duration. In the 2006 Update, the

[3] This software models are available at: http://www.exponent.com/practices/foodchemical/deem.html for DEEM/Calendex; We note that the N-methyl carbamate assessment used three models (DEEM/Calendex, LifeLine, and CARES) to assess exposure and that all three models produced similar results.

Agency has elected to present the single day and 21-day rolling average analyses for food and 21-day rolling average analysis for drinking water, residential, and multi-pathway. Moreover, as described in detail in the risk characterization chapter and due to the extensive cancellation of OP residential uses, the magnitude and pattern of food exposures are the key consideration in evaluating whether the single day, the 21-day rolling average, or the combination of the two best describes the cumulative risk to the OPs. The Agency has concluded that the 21-day rolling average approach is the more appropriate analysis. Results of biomonitoring studies suggest that humans are regularly exposed to OPs. The application of the steady state cholinesterase data matched with the 21-day rolling average is considered a better approximation of actual human exposures when evaluating the cumulative risk to the common mechanism group. Moreover, due to the conservative assumptions included in the CRA, the 21-day rolling average approach is not expected to underestimate residual ChE inhibition which could occur between OP exposures and thus provides a reasonable estimate of cumulative risk to the OPs. Comparison of the steady state cholinesterase data with the single day exposures in food is believed to overestimate the cumulative risk from exposure to this group.

To evaluate the relationship between the single day and 21-day rolling average approaches and to ensure that the risk to the OPs derived from potential acute, peak exposures were not underestimated, the Agency conducted a sensitivity analysis for a group of OPs shown to be the largest contributors to the food assessment. This analysis involved collecting acute brain cholinesterase inhibition data for a subset of OPs to determine the appropriate PoD, making conservative assumptions about the uncertainty and extrapolation factors, and calculating MOEs from single day exposures. Overall, this analysis showed that cumulative risk from acute exposures was not a concern and further supported the health protective nature of the CRA.

Table ES-1 summarized information on the pesticides considered in this assessment and the exposure pathways which were evaluated. The approach for each pathway of exposure and results for the OP cumulative risk assessment are explained and detailed below:

Food

The food component of the OP cumulative risk assessment is considered to be highly refined and to provide reasonable estimates of the distribution of exposures across the US. The exposure estimates for food are based on residue monitoring data from the USDA's Pesticide Data Program supplemented (qualitatively) with information from the Food and Drug Administration (FDA) Surveillance Monitoring Programs and Total Diet Study. The PDP data provide a very reliable estimate of pesticide residues in the major children's foods and account, directly or indirectly through the use of commodity surrogates, for more than 90-95% of consumption for children. These data also provide direct measures of co-

occurrence of OP pesticides in the same sample, alleviating much of the uncertainty about co-occurrence in foods that are monitored in the program. PDP samples with non-detectable residues were treated in this assessment as "zero" values and only residue data from composite samples were utilized in this assessment. Previous analyses have determined that neither of these approaches results in underestimating exposures at the upper percentiles for the OPs (i.e., those percentiles which are of the greatest regulatory importance). For those foods not monitored in PDP, similar commodities that are measured by PDP served as surrogate data sources. This approach is considered to be reasonable and generally sound given that it is based on the concept that families of commodities with similar cultural practices and insect pests are likely to have similar pesticide use patterns and residue levels.

The reliability of the food component of this assessment is also supported by the use of the food consumption data from the USDA's Continuing Survey of Food Intakes by Individuals, 1994-1996/1998 (CSFII). The CSFII surveyed more than 20,000 individuals over two non-consecutive days and provides a detailed representation of the food consumption patterns of the US public across all age groups, during all times of the year, and across all 50 states. Thus, EPA has confidence that the distribution of risk estimates for food is well-predicted and reasonably reflects risks to the US population. The following age groups were analyzed: infants (children <1); 1 and 2 years old (i.e, 1 to < 3 years of age); 3 through 5 years old (i.e., 3 to <6 years of age); 20 through 49 year olds (i.e., 20 to <50 years of age); and 50 years of age and greater. These age groups were selected since they provide a broad representation of potential exposures and because these include age groups that are commonly shown to be the most highly exposed in single-chemical assessments.

In evaluating exposure through food, OPP concludes that a few uses of OP pesticides on food crops generally play a larger role in the results of the food risk assessment. These include: methamidophos/ acephate on beans, watermelon and tomato; and phorate on potato. However, evaluation of the total risk from exposure to OPs in foods indicated that the cumulative MOEs from exposure to OPs do not raise a concern with respect to the 21-day rolling average period. Specifically, MOEs from the 21-day rolling average approach range from 99 for the most exposed subgroup (children 3-5) to 300 for youths 13-19. These MOEs are based on all available PDP data (i.e., 1994 through 2004). Using only the most recent PDP data (2000-2004) for the MOEs for the children 1-2 and 3-5 increase to 111 and 103, respectively. The use of only the most recent PDP data might be considered to be more reflective of current exposure levels and provide added certainty that risks are below the Agency's level of concern using only the most recent residue data for pesticides in foods.

Even when considering the single day exposures when compared to the RPFs and PoDs derived from 21-day steady state cholinesterase data which will tend to overestimate risks, OPP notes that MOEs reach the target MOE of 100 at the 99.3th percentile of exposure for children 1-2 years old, the most highly exposed age group in the single day analyses. As discussed above, the Agency also performed a sensitivity analysis to evaluate the relationship between the single day and 21-day rolling average approaches and to ensure that the risk to the OPs derived from potential acute, peak exposures were not underestimated. Under this conservative acute analysis, the most highly exposed age group reached MOEs equal to 100 at the 99.69th percentile.

Water

The drinking water assessment focuses on areas where combined OP exposure is likely to be among the highest within each of seven regions across the U.S. as a result of total OP usage and vulnerability of drinking water sources. This analysis is based on a probabilistic modeling approach that considers the full range of data and not a single high-end estimate. Exposures in drinking water to individuals are incorporated into the cumulative exposure assessment on a regional- and source water-specific basis (i.e., ground water and surface water, by region). The regional drinking water exposure assessments are intended to represent exposures from vulnerable drinking water sources resulting from typical OP usage and reflect seasonal variations as well as regional variations in cropping and OP use. Each regional assessment focuses on areas where combined OP exposure is likely to be among the highest within the region as a result of total OP usage, adjusted for relative potencies, and vulnerability of the drinking water sources. For ground water, shallow private wells in highly permeable soil and vadose zone materials are expected to be most vulnerable. For surface water, drinking water reservoirs in small, predominantly agricultural watersheds are likely to be most vulnerable.

The co-occurrence of OP residues in water is primarily estimated by means of modeling. Monitoring data are not available consistently enough to be the sole basis for the assessment. However, monitoring data are used to corroborate the modeling results and have helped confirm locations of potentially vulnerable drinking water sources. Specifically: modeling estimates were also compared with available water monitoring data in the 2002 OP CRA (USEPA, 2002); while estimated concentrations of some individual OP pesticides were less than reported detections, most were on the same order or greater than those found in monitoring studies. Subsequent risk management actions (cancellations, rate reductions, etc.) have resulted in lower cumulative OP concentrations in most regions.

Fate and transport properties of the OP pesticides, available monitoring data, and individual chemical assessments indicate that OP residues are not expected to occur in appreciable levels in ground water sources of drinking water. For surface water sources of drinking water, OP residues are expected to reach single- to sub-parts per billion (ug/l) during periods of high-volume runoff following application. These peak concentration periods are generally of short duration (days to weeks).

Based on this drinking water exposure assessment, cumulative OP exposures from drinking water are generally expected to be below levels of concern and are at levels that are not likely to contribute substantially to the multi-pathway cumulative exposure. The one potential exception is Region A (Florida) in which estimated peak concentrations of total phorate residues (parent plus sulfoxide and sulfone transformation products) from use on sugarcane resulted in MOEs near 80 for children 1-2 years old at the 99.9th percentile of exposure for a brief period (16 days). Nevertheless, actual exposures from phorate residues in drinking water are expected to be substantially lower for a variety of reasons that are described in more detail in Section I.E of this document. The Agency is requiring that the drinking water monitoring be performed to confirm that actual drinking water concentrations are not of concern.

Residential

Applications of OP pesticides in and around homes, schools, offices, and other public areas may result in potential exposure via the oral (due to hand-to-mouth activity by children), dermal, and inhalation routes. There are 8 OP chemicals with currently registered residential uses considered as part of the OP 2006 Update in the residential/non-occupational exposure pathway assessment. These are registered for lawn and turf uses, home garden uses, wide-area public health uses, indoor uses (including aerosol sprays and pest strips), and pet uses. Several reliable data sources were used to define how pesticides are used, how quickly the residues dissipate, how people may come into contact with pesticides (e.g., via dermal or inhalation exposure), and the length of time people might be exposed based on certain activities (e.g., playing on a treated lawn). As with the drinking water assessment, the residential exposure assessment considers seasonal applications and timing as well as regional differences. In the case of regional differences, OPP developed one generic regional analysis that included all OP residential uses. This “composite” region (referred to as "Region X") provides a worst-case combination of all OP residential uses and includes worst-case assumptions regarding percent of households treated and application frequency. Thus, this update provides a conservative assessment of risk for which exposures are expected to be higher than would be potentially seen in any single region in the U.S.

The results of the residential risk assessment indicate that remaining uses of OPs in a residential setting are anticipated to provide only small contributions to the cumulative risks from OP pesticides, with the exception of pest strips containing DDVP. However, changes to DDVP registrations which have recently been requested and formalized are expected to substantially reduce estimated exposures and associated risks and significantly decrease the contribution of DDVP to the cumulative risk. Consequently, risks associated with these strips – as borne out by the analyses here -- are now considered to be below OPP's level of concern.

Combined Pathway (Cumulative) Assessment:

EPA also evaluated total MOEs for all three pathways (food + water + residential) considered simultaneously. Evaluating exposures is significantly more complex when the analyses address the simultaneous exposures to more than one pesticide and when distributional inputs derived from data from surveys and monitoring studies – as opposed to default assumptions or point estimates -- are used. The detailed outputs from this OP cumulative assessment allow in-depth analysis of interactions of data sets to estimate the possible risk concerns and identify the sources of exposures. This practice permits expression of the full range of values for each parameter and results in an improved ability to interpret the complete risk picture. Based on the simultaneous evaluation of all three exposure pathways and their associated routes, the MOEs at the 99.9th percentile are approximately 100 or greater for all populations for the 21-day average results from Calendex. The only exception is a brief period (roughly 2 weeks) where drinking water exposures resulting from phorate use on sugarcane result in MOEs near 80 for children 1-2 years old. However, for reasons described in the water exposure pathway section above and in more detail in the main text, actual exposures through drinking water are expected to be much lower in this region. The Agency is requiring that the drinking water monitoring be performed to confirm that actual drinking water concentrations are not of concern. Generally, exposures through the food pathway dominate total MOEs, with exposures through drinking water substantially less throughout most of the year. Residential exposures are substantially smaller (with MOEs exceeding 150 for all scenarios) than exposures through both food and drinking water, with inhalation exposures from DDVP dominating this pathway.

Oxon Formation:

The Agency is aware that a number of OP pesticides may be transformed in the environment to oxons. Limited data also suggest that oxons may be more toxic than the parent OP. With respect to the exposure estimates from food, PDP tests for many oxon metabolites of the OP pesticides. The majority of these oxons have not been found in detectable amounts in the food commodities sampled. Chemical-specific toxicity data has been explicitly incorporated into the assessment for the one oxon that has been consistently

found in detectable amounts in PDP samples, omethoate, the dimethoate oxon. All other OP oxon residues contribute an insignificant amount to the overall food exposure.

Available studies confirm the potential for ten OPs to form stable oxons as a result of standard drinking water treatment. Limited information is also available to indicate that three of the OP pesticides with residential uses may also degrade to oxons. In order to evaluate the potential effects of these transformations on the OP CRA, OPP has conducted a number of sensitivity analyses which are described in the document. Based on the sensitivity analyses conducted for oxon exposure through the residential and drinking water pathways, OPP concludes that the potential for formation of oxons will not substantially alter the risk estimates provided in this assessment. The Agency will be requesting toxicity data on methidathion oxon to further refine estimates for this chemical. Although the Agency believes that the assumptions applied in its sensitivity analysis to this oxon characterization are conservative and that actual exposures are expected to be less than estimated, the data are insufficient at this point to develop and incorporate quantitative determinations of this potential into our baseline assessment.

Conclusion:

The Agency has developed a highly refined and complex cumulative risk assessment for the OPs that represent the state of the science regarding existing hazard and exposure data, and the models and approaches used. Interpretation of the risk estimates presented in this updated OP CRA depends upon the synthesis and processing of a vast body of data on hazard and exposures and no single value in the assessment should be used to independently arrive at the interpretation of the risk estimates or results. EPA continues to have confidence -- as demonstrated by this assessment -- in the overall safety of our food supply and emphasizes the importance of eating a varied diet rich in fruits and vegetables. The Agency has undertaken extensive risk mitigation and risk reduction efforts over the last several years for many OPs through the single chemical aggregate risk assessments. Based in large part on these efforts, the cumulative risks from food, water, and residential exposure to OPs are at or above the target MOE of 100 and therefore do not exceed the Agency's level of concern.

In making its reasonable certainty of no harm finding for individual chemical decisions, EPA gave detailed consideration to what population percentile or what range of percentiles assured protection to all major identifiable subgroups of consumers. In estimating acute risk, EPA has generally relied on a range of different percentiles of the population's exposure, depending primarily on the conservativeness of the inputs to its exposure assessment. For exposure assessments that rely on highly conservative estimates of pesticide residues, EPA has generally based its safety determinations on the estimated exposure of the 95th percentile of the population. For highly refined exposure assessments,

EPA has used the 99.9th percentile as a starting point in assessing safety. Office of Pesticide Programs, US EPA, Choosing a Percentile of Acute Dietary Exposure as a Threshold of Regulatory Concern (March 16, 2000). In no instance is the reliance on such a population percentile a conclusion by EPA that some percentage of the population does not warrant protection; rather, reference to a population percentile is a means to properly characterize, or at least not underestimate, actual exposure of major, identifiable subgroups.

With the OP cumulative risk assessment, EPA has estimated the MOE based on three population percentiles: 95th; 99th; and 99.9th. Leaving to one side the issue of whether there are characteristics intrinsic to a cumulative assessment, as compared to an individual pesticide aggregate, assessment that factor into choice of a population percentile, EPA has focused primary attention on the 99.9th percentile of exposure because most of the inputs and models used to develop the OP cumulative assessment are consistent with a highly-refined risk assessment. Nonetheless, EPA's policy recommendation for use of 99.9th percentile as a starting point for refined probabilistic assessments is only partially applicable to the current assessment given its incorporation, in some instances, of unrefined estimates of residue levels in drinking water. Building on its policy of the use of population-based exposure percentiles in making safety determinations, EPA has evaluated the appropriateness of that percentile taking into consideration two factors: (1) the level of confidence EPA has in its exposure estimates, and the extent to which such estimates may overstate (or understate) potential exposure because they incorporate conservative assumptions or rely on atypical and unrealistic data; and (2) the degree of public health protection incorporated into the determination of the hazard assessment.

Two population groups have calculated MOEs that fall below the target MOE of 100: children aged 3-5 nationwide (having a MOE of 99) and children aged 1-2 and 3-5 in southern Florida (having a MOE of 61). Below is a discussion of the factors the Agency considered in determining the appropriate percentiles upon which to base its safety determination for the OP CRA.

Level of confidence in exposure estimates:

As detailed above, most parts of this assessment are highly-refined in that the food component, which is the pathway responsible for the largest amount of exposure, relies on food residue monitoring data for all but a very few commodities. Nonetheless, there are several conservatisms which are important to take into account, both with regard to the children nationwide and the southern Florida children subgroup. First, there is one generic factor in the risk assessment that tends to make the exposure assessment more conservative: namely, the use in the models of only two days of reported food consumption to estimate exposure by the food pathway over a 21 day period. In effect, the exposures assume that each person consumes one or the other of the two reported diets on any given day during the exposure period of interest.

This contrasts with our typical single-day acute aggregate assessments in which only one of the reported diets is used for each individual. To the extent that one or both days of a person's reported food consumption in the OP CRA includes large amounts of the commodities associated with the more risky OPs, that person will be more likely to appear near the upper end of the distribution of exposures. Such an estimate would properly characterize that person's risks if his or her diet on most days included large amounts of the commodities associated with the risky OPs. Based on our collective experience and common sense, the Agency thinks that such eating patterns are unlikely for a significant portion of the consuming public and would tend to overestimate exposure at the high end exposure percentiles. Most people have more variety in their diets. To the extent that happens, such people would receive less cumulative exposure to OPs and their true risk would be lower than indicated by the quantitative calculations in this assessment.

Second, as to the Florida children subgroup, the lower MOEs for this subgroup are driven almost exclusively by the projected residue values in drinking water for approximately 16 days of the year. There are several reasons to believe that the residue values in water are a significant overestimate of exposure. First, these residues, primarily from the use of phorate on sugarcane, include the transformation products phorate sulfoxide and sulfone; all of which have relatively short half-lives and therefore degrade as they move from water retention structures and drainage canals to surface water systems used for drinking water. Second, there is likely dilution of the estimated concentrations as the water containing these residues mix with larger bodies of water used for drinking water purposes. Third, the model inputs used to determine levels assumed that all phorate applications to sugarcane occur on the same day, which is not likely. Fourth, laboratory studies indicate that phorate and its sulfone and sulfoxide transformation products are likely to break down rapidly (within 24 hours) during chlorination in the drinking water treatment plant. Finally, as discussed in the characterization chapter describing the methodology for estimating potential exposure via the drinking water pathway, the overall approach to generating these estimates incorporates a number of conservative assumptions designed to prevent an underestimate of exposure. Collectively, these assumptions are very likely to overstate significantly the contribution to overall risk resulting from consumption of drinking water during the 16 day period identified as part of the Southern Florida scenario.

The degree of public health protection in the hazard assessment:

There are two significant sources of overprotection in the cumulative hazard assessment. The Agency has elected to use 10% inhibition in brain ChE as the response level for the RPFs and PoDs. The 10% response level is health protective in that no functional or behavioral

effects have been noted below this level in adult or juvenile animals. Thus the 10% response level provides a point where functional or behavioral neurotoxicity is not expected. Second, in the food risk assessment use of the 21-day steady state BMDs to calculate the RPFs is overly conservative when evaluating one-day exposures since BMDs derived from acute toxicity studies are 2-10X higher than those for steady state exposures for most OPs.

Additionally, EPA believes it is relevant to examine the MOEs at values slightly below the 99.9th percentile in determining the significance of the MOE calculations at the 99.9th percentile. The use of the 95th and 99.9th percentile in assessing safe exposure, similar to the use of 10X safety factors in estimating the safe dose, is not a practice that arose from a precise mathematical calculation based on empirical data. Rather, the 95th and 99.9th percentiles, just like the 10X safety factors, are rules of thumb based on long experience of working with complex exposure and toxicity data sets. Given this origin, EPA is wary of treating the 99.9th percentile as an immutable, precise standard and thinks there is value in considering at what percentile of the estimated exposure distribution subgroups that fall below the target MOE of 100 at the 99.9th percentile reach an acceptable MOE. For the two groups in question here – children nationally aged 3-5 and Florida children aged 1-5 – the target MOE is reached at greater than the 99.89th percentile and between the 99.5th and 99.75th percentiles, respectively.

Taking all of these factors into account, EPA finds that there is a reasonable certainty of no harm to all major, identifiable population subgroups from cumulative exposure to the OPs. Nearly all the subgroups equal or exceed the target MOE of 100 at the 99.9th percentile of exposure. For children aged 3-5, even if an MOE of 99 is different than 100 for risk assessment purposes, it cannot be considered to indicate a risk of concern. The conservatisms in the exposure assessment and in the calculation of the RPF more than offset any theoretical concern. The MOEs for the Florida children subgroup cannot be dismissed as simply indistinguishable from the target MOE. On the other hand, not only do the general conservatisms in the exposure and toxicity assessments apply to this group but, most importantly, the driver in the risk calculation for this group is the highly conservative estimate of residues in drinking water. EPA's policy of choosing population percentiles only recommended use of the 99.9th percentile as a starting point when dealing with highly refined residue estimates – not situations involving a mixture of refined and unrefined residue estimates where the residue driving the risk estimate is the unrefined residue estimate. Thus, EPA finds that both of these groups have a reasonable certainty of no harm from cumulative exposure to the OPs as well.

Given this determination, the Agency concludes that the results of the OP CRA support a reasonable certainty of no harm finding as required by FQPA and therefore EPA has completed reassessment of the OP tolerances.

Table ES-1 OP Pesticides Considered in the 2006 Update of the OP CRA

CHEMICAL	FOOD	WATER	RESIDENTIAL
Acephate	X	X	X
Azinphos- methyl (AZM)	X	X	
Bensulide		X	X
Cadusafos			
Chlorethoxyphos	X	X	
Chlorfenvinphos			
Chlorpyrifos	X	X	
Chlorpyrifos-methyl	X		
Chlorthiophos			
Coumaphos			
DDVP	X	X	X
Dialifor			
Diazinon	X	X	
Dicrotophos		X	
Dimethoate	X	X	
Dioxathion			
Disulfoton	X	X	X
Ethion			
Ethoprop	X	X	
Ethyl Parathion			
Fenamiphos			
Fenitrothion			
Fenthion			
Fonofos			
Fosthiazate	X		
Isazophos			
Isofenphos			
Malathion	X	X	X
Methamidophos	X	X	
Methidathion	X	X	
Methyl Parathion	X	X	
Mevinphos	X		
Monocrotophos			
Naled		X	X
Oxydemeton-methyl (ODM)	X	X	
Phorate	X	X	
Phosalone	X		
Phosmet	X	X	
Phosphamidon			
Phostebupirim		X	
Pirimiphos-methyl	X		
Profenofos	X	X	
Propetamphos			
Sulfotepp			
Sulprofos			
Temephos			
Terbufos	X	X	
Tetrachlorvinphos	X		X
Tribufos (def)	X	X	
Trichlorfon			X

List of Acronyms

APA	Apple Processors Association
AChE	Acetycholinesterase
AZM	Azinphos Methyl
BMD	Benchmark dose (or **BMD_{10}**)
BMDL	Lower limit on the benchmark dose (or **$BMDL_{10}$**)
CAG	Cumulative Assessment Group
CELs	Comparative Effect Levels
CHAD	Consolidated Human Activity Database
ChE	Cholinesterase
CMG	Common Mechanism Group
CNS	Central Nervous System
CRA	Cumulative Risk Assessment
CSFII	USDA's Continuing Survey of Food Intake by Individuals
CWS	Community Water Systems
DDVP	Dichlorvos
DEEM-FCID	Dietary Exposure Evaluation Model
DFR	Dislodgeable Foliar Residue
EAA	Everglades Agricultural Area
EFED	Environmental Fate and Effects Division
FDA	Food and Drug Administration
FIFRA	Federal Insecticide, Fungicide, Rodenticide Act
FQPA	Food Quality Protection Act
FR	Federal Register
GoF	Goodness of Fit
HED	Health Effects Division
HSRB	Human Studies Review Board
LCO	Lawn Care Operator
LOAEL	Lowest Observable Adverse Effect Level
LOC	Level of Concern
LOD	Limit of Detection
LOQ	Limit of Quantification
MBS	Market Basket Study
MOE	Margin of Exposure
MRID	Master Record Identification Number
NASS	National Agricultural Statistics Survey
NHANES	National Health and Nutrition and Examination Survey
NHANES III	Third National Health and Nutrition Examination Survey
NAWQA	USGS National Water-Quality Assessment Program
NHEXAS	National Human Exposure Assessment Survey
NHGPUS	National Home and Garden Pesticide Use Survey
NOAELs	No-Observed-Adverse-Effect-Levels
OPs	Organophosphorus Pesticides
OP CRA	Organophosphorus Pesticide Cumulative Risk Assessment
OPP	The EPA's Office of Pesticide Programs

ORETF	Outdoor Residential Exposure Task Force
ORD	Office of Research and Development
PBPK	Physiologically Based Pharmacokinetic
PCA	Percent Crop Area
PCO	Pest Control Operator
PCRA	Preliminary Cumulative Risk Assessment
PDP	Pesticide Data Program (USDA)
PHED	Pesticide Handler Exposure Database
PoD	Point of Departure
PK	Pharmacokinetic
PNS	Peripheral Nervous System
PRZM-EXAMS	Pesticide Root Zone Model- Exposure Analysis Modeling System
RBC	Red Blood Cell
REJV	Residential Exposure Joint Venture
RPF	Relative Potency Factor
SAP	FIFRA Scientific Advisory Panel
SFWMD	South Florida Water Management District
SLN	Special Local Need
SOP	Standard Operating Procedure
TCVP	Tetrachlorvinphos
TDS	Total Diet Study
TTR	Turf Transferable Residues
UE	Unit Exposure
USDA	United States Department of Agriculture
WOE	Weight of the Evidence

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I. OP Cumulative Assessment – 2006 Update

A. Introduction

1. Background

The Food Quality Protection Act of 1996 significantly amended the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) and the Federal Food, Drug, and Cosmetic Act (FFDCA). One of the major changes imposed by FQPA was to require EPA to consider the cumulative effects of chemicals with a common mechanism of toxicity in its tolerance reassessment decisions.

The organophosphates (OPs) are a group of closely related pesticides that affect functioning of the nervous system. The OPs were included in the Agency's first priority group of pesticides to be reviewed under FQPA. In 1999, EPA determined that the OPs form a common mechanism group based on their shared ability to bind to and phosphorylate the enzyme acetylcholinesterase in both the central (brain) and peripheral nervous systems (USEPA, 1999). As such, the OPs require a cumulative risk assessment under FQPA.

To meet the requirements of FQPA, EPA developed methodologies for conducting cumulative risk assessments, and prepared a cumulative assessment for the OPs. The Office of Pesticide Programs (OPP) has published guidance on conducting cumulative risk assessments. This guidance has been reviewed by the FIFRA Scientific Advisory Panel (SAP). The revised guidance is available on EPA's website at http://www.epa.gov/pesticides/trac/science/cumulative_guidance.pdf.

EPA consulted with the SAP to obtain expert review, advice, and recommendations at each major step in the development of the OP cumulative risk assessment and the underlying methodologies. EPA held numerous external peer-review meetings with the SAP and asked for comment on many issues, including its approaches to grouping chemicals based on a common mechanism of toxicity; OPP's guidance for conducting cumulative risk assessment; methods and approaches for dose-response and exposure assessment; and probabilistic exposure models for combining food, drinking water, and residential exposure pathways.

The Agency also held numerous meetings with the FQPA Federal Advisory Committees TRAC (Tolerance Reassessment Advisory Committee) and CARAT (Committee to Advise on Reassessment and Transition), which were established under the Federal Advisory

Committee Act (FACA). Various stakeholders including public interest groups, state agricultural agencies, pesticide industry representatives, growers, USDA, and others were represented on these committees. The Agency sought advice, comments, and recommendations on the methodologies and framework which were to guide the implementation of FQPA and tolerance reassessment

Beginning in July 2000 through June 2002, the Agency held several technical briefings with the public to discuss issues related to the cumulative technical guidance document, hazard and dose-response assessment, exposure assessment, and the Preliminary and Revised cumulative risk assessments. EPA issued the Preliminary OP Cumulative Risk Assessment in December 2001. The Agency solicited comment on the preliminary assessment for 90 days. EPA released the Revised OP Cumulative Risk Assessment in June 2002, and public comments were accepted for 30 days. The previous versions of the cumulative assessment are available on EPA's website at www.epa.gov/pesticides/cumulative.

In this 2006 Update to the OP Cumulative Assessment, EPA has evaluated potential risk associated with more than 30 organophosphates, taking into account food, drinking water and residential uses. EPA has employed methodologies to account for variability in potential exposures based on age as well as seasonal and geographic factors. The assessment relies on a large variety of data sources, such as monitoring data that measure pesticide residues found in food, in order to obtain the most realistic estimates of actual exposure to the population from the OPs.

2. Major Differences between the 2002 Revised OP Cumulative Assessment and the OP Cumulative Risk Assessment (2006 Update)

During the four years since the issuance of the 2002 Revised OP Cumulative Risk Assessment, EPA has been working to further improve and refine its assessment of the cumulative risks associated with the OPs. These refinements include changes to incorporate the most recent food residue data, to reflect the Agency's review of new data in juvenile animals, and to consider the potential for direct exposure to the oxon degradates. In addition, the Agency has updated the assessment to reflect risk mitigation measures and other use pattern changes for individual OPs since the Revised OP Cumulative Assessment was issued in June 2002. The major differences between the 2002 Revised OP Cumulative Risk Assessment and the OP Cumulative Risk Assessment (2006 Update) are discussed below.

a. Hazard Assessment

i. Intra-species Variability and Inter-species Extrapolation Factors

EPA typically applies default 10X uncertainty factors in its risk assessments to account for inter-species (i.e., animal to human) extrapolation and intra-species (i.e., within human) variability in the absence of specific data to refine them. In May 2006, the Agency presented its evaluation of the azinphos methyl (AZM) and DDVP repeated-exposure human toxicity studies to the Human Studies Review Board (HSRB). The HSRB concurred with the Agency's proposal that neither study was appropriate to refine the inter-species extrapolation factors used in the OP cumulative assessment. Regarding intra-species extrapolation, there are not sufficient data at this time to support refining this uncertainty factor. For more information, please refer to the hazard chapter of this document (Section I.B).

ii. Chemical-specific FQPA Safety Factors

FQPA directs EPA, in setting or reassessing pesticide tolerances, to use an additional 10X safety factor to protect infants and children, taking into account the potential for pre- and post-natal toxicity and the completeness of the toxicology and exposure databases. The statute authorizes EPA to modify this 10X FQPA safety factor only if reliable data demonstrate that the resulting level of exposure will be safe for infants and children.

The Agency presented its preliminary analysis regarding the sensitivity of the young and the FQPA 10X factor for the OP cumulative assessment to the FIFRA SAP in June 2002. Based on the comments from the SAP and the public, the Agency has revised its approach. In the current risk assessment, EPA retained the 10X FQPA safety factor for most of the OPs. New data evaluating the relative sensitivity of juvenile and adult rats have been submitted to allow the Agency to refine the FQPA safety factors for 13 OPs. For each of these, the Agency reviewed a repeated dosing, comparative cholinesterase study that justified either retention or reduction of the 10X FQPA safety factor. EPA concluded that a reduction in the FQPA safety factor was appropriate for 10 of the 13 OPs for which appropriate data were reviewed. For more information, including a list of the chemical-specific FQPA safety

factors, please refer to the hazard chapter of this document (Section I.B).

b. Updates to the Food Exposure Data

The OP cumulative assessment uses residue data from the U.S. Department of Agriculture Pesticide Data Program (PDP). The Revised OP Cumulative Assessment used PDP data from 1994-2001. The OP Cumulative Assessment (2006 Update) adds PDP data from 2002-2004. The food processing factors were also updated, where appropriate, to include the additional PDP commodities from the 2002-2004 data. For more information, please refer to the food chapter of this document (Section I.C).

c. Potential for Direct Exposure to Oxons

Some of the OPs form oxon transformation products as a result of drinking water chlorination. In the 2006 Update to the OP Cumulative Assessment, EPA considered the potential for direct oxon exposure in the food, residential, and drinking water exposure assessments. EPA used a tiered approach to evaluate the risks from the oxon-forming OPs. For more information, please refer to the hazard and water chapters of this document (Sections I.B and I.E).

d. Mitigation Measures

During the four years since the issuance of the Revised OP Cumulative Assessment in June 2002, the Agency imposed risk reduction measures on some of the major contributors to OP cumulative risk, as discussed below. The risk estimates presented in the OP Cumulative Risk Assessment (2006 Update) reflect the risk mitigation measures taken on individual OPs since FQPA was signed into law in August 1996. A table summarizing these mitigation measures is provided in Appendix II (Table II.A.1 1).

i. Food

The mitigation measures summarized in Table II.A.1 1 have been accounted for in the food exposure assessment. Mitigation imposed on dimethoate resulted in the most significant reductions in food risk.

Dimethoate. In July 2005, the use of dimethoate was voluntarily cancelled on seven crops (apples, broccoli raab, cabbage, collards, grapes, head lettuce, and spinach) (70 FR 41717; July 20,

2005). Three of the cancelled uses – apples, grapes, and spinach – were major contributors to OP cumulative dietary risk. The OP Cumulative Assessment (2006 Update) reflects the cancellation of these uses.

Azinphos-methyl. In June 2006, the Agency issued its proposed decision to phase-out all remaining uses of AZM. Some uses are scheduled to be phased-out by 2007, and the remaining uses are scheduled to be phased-out by 2010. A Federal Register (FR) notice announcing this decision and soliciting public comments was published on June 9, 2006 (71 FR 33448). The Agency has evaluated OP cumulative risks two ways – with the remaining AZM uses included and excluded. The OP Cumulative Assessment (2006 Update) reflects the termination of these uses, but also contains discussion about the results if the AZM uses are included in the assessment.

The public comment period for EPA's proposed decision on AZM is scheduled to close on August 8, 2006, which is after the issuance of this document. If the Agency receives public comments during the comment period that lead it to revisit its decision to phase-out all remaining uses of AZM, the OP cumulative assessment will be revised as necessary.

ii. Residential

The residential uses summarized in Appendix II.A.1 1 have been accounted for in the residential exposure assessment for the OP Cumulative Assessment (2006 Update).

DDVP. In May 2006, the technical registrant for DDVP voluntarily requested changes to many of the residential uses of DDVP, including:

- Cancellation of the 100 gram pest strip;
- Cancellation of the 21 gram pest strip (contingent upon registration of a new 16 gram pest strip);
- Cancellation of the total release fogger;
- Cancellation of use on lawns, turf, and ornamentals; and
- Cancellation of crack and crevice uses.

The above changes resulted in reductions in OP cumulative residential risk. The OP Cumulative Assessment (2006 Update) reflects these changes to the DDVP residential use patterns.

iii. Drinking Water

Since the Agency's issuance of the Revised OP cumulative risk assessment in June 2002, usage practices for a number of the OPs have changed as a result of EPA's risk management decisions. The phase-out of all remaining azinphos methyl uses and cancellation of some uses for dimethoate, diazinon, and methamidophos resulted in reductions to the estimated cumulative OP exposures from drinking water sources. However, the overall exposure estimates in the OP Cumulative Assessment (2006 Update) are similar to those estimated in the 2002 Revised OP Cumulative Risk Assessment.

3. Scope of the OP Cumulative Risk Assessment (2006 Update)

The OP Cumulative Assessment (2006 Update) is an update to the 2002 Revised OP Cumulative Assessment. The same approaches, methods, and models for dose-response assessment, food, water, and residential exposure, along with multi-pathway (i.e., cumulative) assessment used in the 2002 Revised OP Cumulative Assessment have been used here. As such, detailed descriptions of these methods and/or models are not included in the following chapters. The reader should refer to the 2002 Revised OP Cumulative Assessment for more detailed information.

The chapters herein provide summaries of the approaches used, discussion of any new or updated data, results of exposure and risk estimates, and the Agency's conclusions regarding the overall cumulative risk of the OPs. All of the data and/or model inputs used here are provided in Appendices to the OP Cumulative Assessment (2006 Update). Given that this risk assessment is a milestone in the Agency's consideration of tolerance reassessment for the OPs, a complete risk characterization discussion is provided in Section I.G.

B. Hazard / Relative Potency Factor

1. Introduction

Since the passage of the FQPA, OPP has presented proposed guidance, tools and methodologies for conducting cumulative risk assessments to the FIFRA Scientific Advisory Panel (SAP). Specifically, the hazard and dose-response sections of the OP cumulative risk assessment have been presented to the FIFRA SAP four times between 1999 and 2002 including the February 5-8, 2002 meeting on the methods used in the Preliminary Cumulative Risk Assessment (PCRA) of the Organophosphorus Pesticides (FIFRA SAP, 2000a, 2001a, 2001b, 2002a). The Agency's preliminary analysis regarding the relative sensitivity of infants and children for the FQPA 10X factor was reviewed by the SAP in June, 2002 (FIFRA SAP, 2002b). Following the previous SAP reviews, constructive comments and recommendations have been incorporated into revisions and refinements of the hazard and dose-response assessment for the OPs. The current chapter is meant only as an update to the June, 2002 OP cumulative risk assessment. The Agency continues to rely on the Relative Potency Factor approach for quantifying chemical potency and for extrapolating cumulative risk. Relative potency factors (RPFs) for more than 30 OPs were released to the public on April 17, 2002 (http://www.epa.gov/pesticides/cumulative/pra-op/rpf_final.htm). The RPFs and points of departure (PoD) in this update are the same as those reported by the Agency previously. The statistical methods used to derive the RPFs and PoDs are not included in this chapter. The reader is referred to the 2002 revised OP CRA for the details regarding dose-response methods used by the Agency.

The only new information and discussion provided in this udpate include the assignment of chemical-specific uncertainty and extrapolation factors including the Agency's revised FQPA 10X factor analysis and consideration of inter- and intra-species extrapolation. As discussed in the following chapters (food, water, residential), the Agency has also considered the degree to which some OPs may form oxon or oxon sulfoxide/sulfone degradates in the environment which could lead to direct exposure to these chemicals. As part of the OP CRA, a screening assessment has been performed on the impact of direct exposure to oxons from various pathways; this chapter addresses the hazard component of this screening assessment.

2. Endpoints and Toxicology Studies

Before the cumulative risk of exposure to OPs can be quantified, the relative toxic potency of each OP must be determined. The determination of relative toxic potency should be calculated using a uniform basis of comparison, by using, to the extent possible, a common response derived from the comparable measurement methodology, species, and sex for all the exposure routes of interest (USEPA 2001a, 2002a)

As part of the hazard analysis, all relevant responses were evaluated to identify the most appropriate endpoint pertaining to the common mechanism of toxicity and to determine which endpoint(s) provide(s) a uniform and common basis for determining the relative potency of the cumulative assessment group. OPs exert their neurotoxicity by binding to and phosphorylating the enzyme acetylcholinesterase in both the central (brain) and peripheral nervous systems (Mileson et al., 1998). There are laboratory animal data on OPs for cholinesterase activity in plasma, red blood cell (RBC) and brain, as well as behavioral or functional neurological effects in submitted guideline studies. Measures of acetylcholinesterase inhibition in the peripheral nervous system (PNS) are very limited for the OP pesticides. As a matter of science policy, blood cholinesterase data (plasma and RBC) are considered appropriate surrogate measures of potential effects on PNS acetylcholinesterase activity and of potential effects on the central nervous system (CNS) when brain cholinesterase data are lacking (USEPA, 2000a). Behavioral changes in animal studies usually occur at higher doses compared to doses needed to inhibit cholinesterase. Also, behavioral measures are limited in terms of the scope of effects assessed and the measurements employed. Plasma, RBC, and brain cholinesterase inhibition were initially considered potential endpoints for extrapolating risk to humans in the OP cumulative risk assessment.

Humans may be exposed to the OPs through diet, in and around residences, schools, commercial buildings, etc. Therefore, the potency of OPs needs to be determined for the oral, dermal, and inhalation routes of exposure. Cholinesterase inhibition can result from single or short-term exposures. Various toxicokinetic and toxicodynamic factors influence an individual OPs time to peak effect of inhibition, persistence of action following acute exposure, and the duration of exposure required to reach steady state inhibition. OPP has elected to estimate relative potencies and PoDs using measurements where cholinesterase inhibition in the laboratory animal is not changing with time. OPP defines this point where continued dosing at the same level results in no further increase in enzyme inhibition as steady state. The use of cholinesterase data for single-dose or short duration studies to model the comparative potency is

problematic because the extent of inhibition is rapidly changing immediately following dosing. Measures of cholinesterase taken during this time will be highly variable and uncertain. Cholinesterase inhibition will continue to increase until steady state is reached. When the measurements are taken at steady state, the differences in toxicokinetics among the OPs are less likely to impact the assessment. At this point in the dosing scheme, it is possible to develop a stable estimate of relative inhibitory capacity (i.e., relative potency) between compounds.

OPP has elected to use data reflecting steady state conditions to estimate relative potencies for the OPs in the interest of producing RPFs that are reproducible and reflect less uncertainty due to rapidly changing, time-sensitive measures of cholinesterase. OPP has shown previously that steady state is reached by approximately 21 to 28 days of exposure (USEPA, 2001b). No further analysis of the time course data was performed in the revised cumulative risk assessment. The analysis focused on studies of duration of 21 days or greater in order to use cholinesterase data that have attained steady state.

Relative potency should be based whenever possible on data from the same species and sex to provide a uniform measure of relative potency among the chemical members of the cumulative assessment group (USEPA, 2002a). Under FIFRA, toxicology studies in various species (e.g., dog, mouse, rat and rabbit) are submitted to OPP. For the OPs, toxicology studies in the adult rat provided the most extensive cholinesterase activity data for all routes, compartments, and both sexes. Thus, the focus of this analysis was on cholinesterase activity data derived from adult male and (non-pregnant) female rats. EPA used rabbit studies for five chemicals with residential/non-occupational exposure potential because dermal toxicity data in rats were not available.

Studies used in this analysis were identified by their source MRID number. Studies submitted to OPP are reviewed for their quality of cholinesterase measurements and consistency of their experimental protocol with the OPPTS Guidelines (http://www.epa.gov/opptsfrs/home/guidelin.htm).

Oral relative potency values were needed for all OP pesticides included in the CRA because of potential dietary exposures from food and drinking water and hand to mouth exposures associated with residential/non-occupational uses. Numerous oral studies with comparable methodologies were available and suitable for quantitative dose-response analysis. Study type, duration of exposure, number of animals per dose group, sex, compartment, and the measured effect for each dose group (mean cholinesterase activity, activity units, and standard deviation) were compiled into an electronic spreadsheet. In

feeding studies, average pesticide intake (mg/kg/day) over the entire study was used. At least one oral toxicity study of the appropriate duration was available for all the OPs.

Dermal and inhalation relative potency factors were needed for OPs with residential exposure. Unlike the database of oral toxicity studies, the database of dermal and inhalation studies with cholinesterase measurements is limited. Comparative effect levels (CELs) have been used to compare the dermal and inhalation relative potencies of the OPs. CELs are dose levels from a given study with a defined range of effects. The CEL was defined as the dose causing a maximum of 15% brain cholinesterase inhibition. Quantitative dose-response analysis for estimating a common benchmark response as used to calculate oral relative potency values is the preferred method for determining relative potency.

3. Selection of Relative Potency Factors and Points of Departure from the Female Brain ChE Data Set

A key component of cumulative hazard assessment is to select an endpoint pertinent to the common mechanism of toxicity that can be used to quantify cumulative risk. OPP decided to use female brain ChE data for quantifying cumulative risk for OPs. OPP decided to estimate cumulative risk based on RPFs and PoDs from the female brain ChE database for several reasons. Principally, estimates of relative potency based on brain ChE have tighter confidence intervals and therefore will confer less uncertainty on cumulative risk estimates compared to relative potency estimates based on RBC. Also, these data represent a direct measure of the common mechanism of toxicity as opposed to using surrogate measures. The toxic potencies and PoDs for brain cholinesterase inhibition for these OPs are generally similar to the RBC data for the oral, inhalation, and dermal exposures (USEPA, 2001b). Finally, in the present analysis, although male and female rats were equally sensitive for most OPs, female rats were more sensitive to three OPs. Therefore, OPP has chosen to base its RPFs on female brain measurements.

4. Determination of Toxic Potency

a. Determination of Chemical Potency: Oral Route

As described in the guidance document for cumulative risk assessment (USEPA, 2002a), dose-response modeling is preferred over the use of NOAEL/LOAELs (i.e., no or lowest observed adverse effect levels) for determining relative toxicity potency. NOAELs and LOAELs do not necessarily reflect the relationship between dose and response for a given chemical, nor do they reflect a uniform response

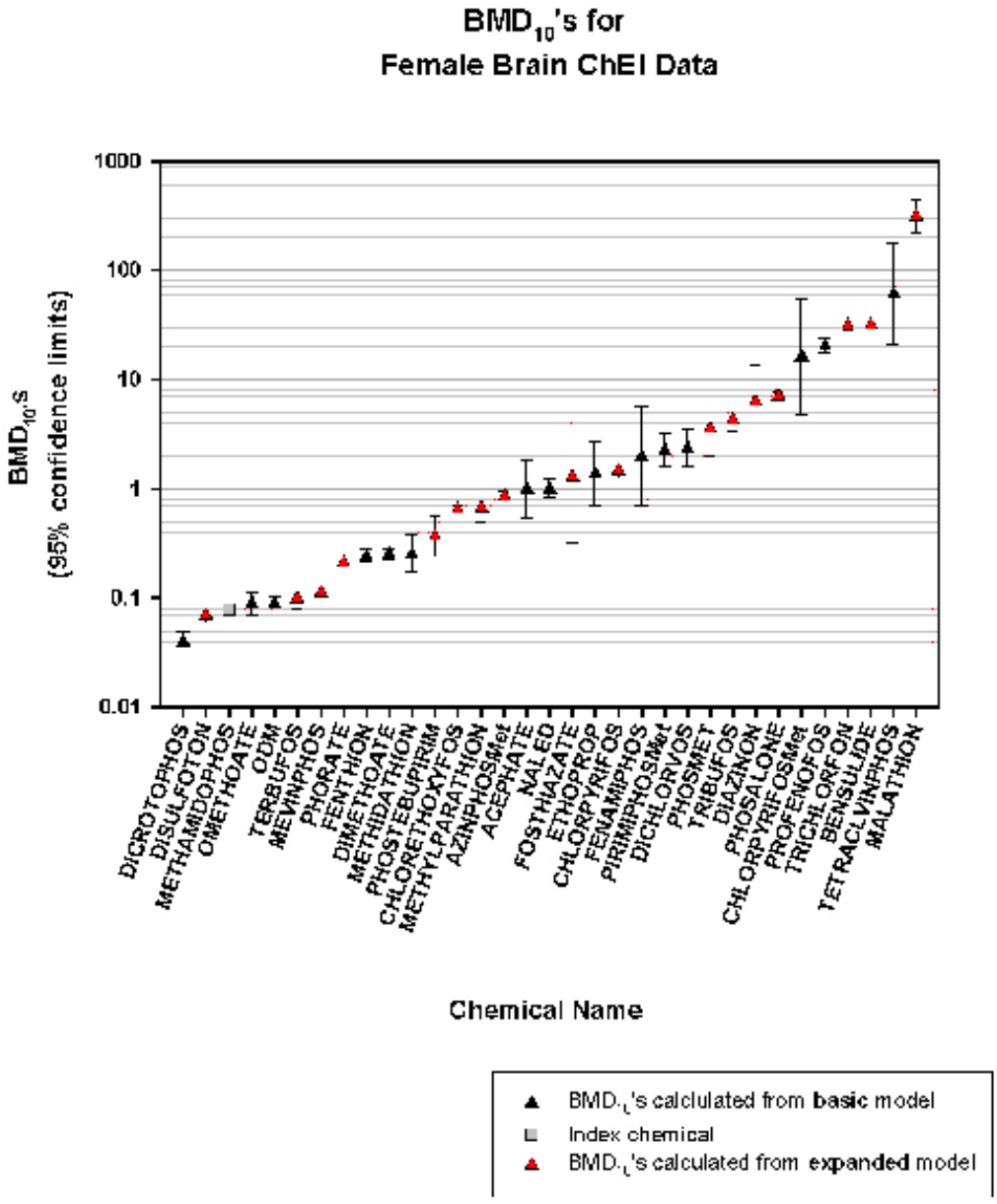
across different chemicals. In the analysis of the oral toxicity data, benchmark dose (BMD) modeling has been used to determine the toxic potency of the OPs. The central estimate on the BMD provides an appropriate measure for comparing chemical potency. In this cumulative risk assessment, the BMD_{10}, the central estimate of a benchmark dose associated with 10% AChEI, was selected as the response level for developing RPFs and PoDs. A PoD is a point estimate on the index chemical's dose-response curve from which risk to the anticipated exposure levels in the human population is extrapolated. The 10% response level is generally at or near the limit of sensitivity for discerning a statistically significant decrease in ChE activity across the brain compartments and is a response level close to the background ChE. As part of EPA's Revised Cumulative Risk Assessment for the OPs, EPA performed a power analysis of brain ChE data available for more than 30 OPs (USEPA, 2002b). The results of the analysis indicated that most studies can reliably detect 10% brain ChE inhibition. Furthermore, in studies available to EPA for the OPs, clinical signs and behavioral effects have not been shown in studies below 10% ChE inhibition.

In the dose-response analysis, the cholinesterase data for various time points for a specific chemical are modeled *together*. The Agency's dose-response analysis is sufficiently flexible to account for ChE inhibition at all tested doses and/or the possibility that the data show a "low dose shoulder." The low dose shoulder corresponds to the portion of the dose-response curve where the slope at the low end of the dose-response curve is flatter compared to the slope at higher doses. Brain ChE for more than 30 OPs were fit to a decreasing exponential model. Detailed information about the empirical modeling for each chemical can be found in the June 2002 OP CRA. BMD and $BMDL_{10}$ (lower 95% confidence limit on the BMD_{10}) estimates are provided in Table I.B-1 and Figure I.B-1 below. A spreadsheet containing the cholinesterase data used to derive the BMD_{10} estimates are contained in Appendix II.B-3.

Table I.B-1 Oral BMD_{10}s and $BMDL_{10}$s from female and male rat brain ChE inhibition for the OPs.

Oral BMD_{10}s and BMDLs (mg/kg/day) estimated for brain ChE activity				
Chemical	Female		Male	
	BMD_{10}	$BMDL_{10}$	BMD_{10}	$BMDL_{10}$
Acephate	0.99	0.53	0.77	0.41
Azinphos-methyl	0.86	0.79	1.14	0.98
Bensulide	31.91	30.44	40.88	37.11
Chlorethoxyfos	0.65	0.61	0.69	0.62
Chlorpyrifos	1.48	1.26	1.50	1.27
Chlorpyriphos-methyl	16.20	4.77	14.26	4.21
Diazinon	6.24	2.89	9.62	5.39
DDVP	2.35	1.61	1.71	0.08
Dicrotophos	0.04	0.04	0.04	0.03
Dimethoate	0.25	0.22	0.35	0.31
Disulfoton	0.07	0.06	0.10	0.09
Ethoprop	1.37	0.70	1.35	0.69
Fenamiphos	1.96	0.69	1.73	0.63
Fenthion	0.24	0.21	0.18	0.15
Fosthiazate	1.28	0.32	1.48	0.38
Malathion	313.91	221.12	212.02	119.31
Methamidophos	0.08	0.07	0.07	0.06
Methidathion	0.25	0.17	0.24	0.16
Methyl-parathion	0.67	0.50	0.70	0.51
Mevinphos	0.11	0.10	0.15	0.13
Naled	1.00	0.82	1.00	0.82
Omethoate	0.09	0.07	0.14	0.12
Oxydemeton-methyl	0.09	0.09	0.07	0.07
Phorate	0.21	0.20	0.29	0.26
Phosalone	6.93	6.27	7.88	7.05
Phosmet	3.56	2.03	4.15	2.25
Phostebupirim	0.37	0.24	0.40	0.26
Pirimiphos-methyl	2.25	1.61	1.58	0.93
Profenofos	20.58	17.64	24.98	21.86
Terbufos	0.10	0.08	0.18	0.17
Tetrachlorvinphos	60.69	20.97	369.27	102.31
Tribufos	4.27	3.31	4.52	3.47
Trichlorfon	31.74	28.62	58.49	45.39

Figure I.B-1 Plot of BMD_{10}s and the 95% confidence limits for female rat brain ChE inhibition for the OPs



b. Determination of Chemical Potency: Dermal Route

Chemical potency was determined using CELs for the dermal route of exposure. These CELs are experimental dose levels which elicit a similar toxicological response to the selected endpoint.

Cholinesterase activity data were collected from dermal toxicity studies for nine chemicals with residential/non-occupational exposure and the index chemical (methamidophos), which has no residential/non-occupational uses[4]. Five OPs were tested by the dermal route in rats. Only rabbit studies were available for the other five OPs. Thus, it was not possible to compare cholinesterase activity data from dermal studies in only one species. Of the chemicals with potential dermal exposure, only three chemicals (acephate, disulfoton, and naled) had more than one dermal toxicology study which could be used for assessing relative potency. One chemical, DDVP, had no dermal toxicity study. The requirement for a dermal toxicity study with DDVP was waived because the volatility of the chemical renders it technically difficult to conduct such a study.

Relative potencies of the chemicals with residential/non-occupational uses were determined by using CELs derived from data on inhibition of cholinesterase activity in female rat brain. The CEL was defined as the lowest dose where a maximum 15% brain cholinesterase inhibition (compared to control) occurred. Table I.B-2 provides CELs for the dermal route.

[4] Note: Residential/non-occupational uses of fenthion and fenamiphos have been cancelled and are not assessed in the exposure assessment.

Table I.B-2 Dermal CELs from rat and rabbit brain and RBC ChE inhibition for the OPs with residential/non-occupational uses.

Chemical	Species	Male Brain CEL mg/kg/day	Male Brain Next Higher Dose mg/kg/day	Female Brain CEL mg/kg/day	Female Brain Next Higher Dose mg/kg/day
Acephate	rat	300 9%	>300* 9%	**300** **14%**	>300* 14%
Bensulide	rat	500[a] 0-9%	>500*[a] 0-9%	**500**[a] **2-10%**	>500*[a] 2-10%
DDVP	Dermal exposure study waived due to volatility of compound.				
Disulfoton	rabbit	1.6 7%	3 55%	**1.6** **8%**	3 27%
Fenamiphos	rabbit	10 * 0%	>10 * 0%	**0.5** **0%**	2.5 18%
Fenthion	rabbit	100 13%	150 65%	**50** **13%**	100 24%
Malathion	rabbit	300[a] 2%	1000[a] 65%	**50**[a] **0%**	300[a] 19%
Methamidophos	rat	0.75 0%	11.2 41%	**0.75** **5%**	11.2 38%
Naled	rat	10 0%	20 60%	**10** **0%**	20 60%
Tetrachlorvinphos	rat	1000 0%	>1000 * 0%	**1000** **0%**	>1000 * 0%
Trichlorfon	rabbit	1000 0%	>1000 * 0%	**100** **4%**	300 18%

* Highest dose tested.

c. Determination of Chemical Potency: Inhalation Route

Chemical potency was determined using CELs for brain cholinesterase activity for the inhalation route of exposure. Cholinesterase activity data were collected from inhalation toxicity studies for seven chemicals with residential/non-occupational exposure and the index chemical (methamidophos). Two inhalation exposure studies were available for acephate whereas only one suitable study was available for the other OPs. There were four whole-body exposure studies, one head-nose study, and three nose only exposure studies. No inhalation toxicity study was available for two chemicals with remaining residential uses (bensulide and tetrachlorvinphos). Inhalation exposure to bensulide has not been assessed as there is minimal chance for outdoor inhalation risk to this OP. For tetrachlorvinphos, the oral RPF was used as a surrogate in the absence of inhalation data. Relative potency was calculated from CELs for brain cholinesterase activity determined from inhalation toxicity studies. The CEL was defined as the lowest dose where a maximal response [brain cholinesterase inhibition] of 15% (compared to control) occurred. Table I.B-3 provides CELs for the inhalation route[5].

[5] Note: Residential/non-occupational uses of fenthion and fenamiphos have been cancelled and are not evaluated in the exposure assessment.

Table I.B-3 Inhalation CELs from rat brain ChE inhibition for the OPs with residential/non-occupational uses.

Chemical	Method	Male CEL (mg/kg/day)	Male Next higher dose (mg/kg/day)	Female CEL mg/kg/day	Female Next higher dose (mg/kg/day)
Acephate	nose only	1.419 14%	1.419* 14%	**1.492** **13%**	1.492* 13%
Bensulide	No inhalation toxicity study was available for bensulide				
DDVP	whole body	0.436 10%	0.436 10%	**0.458** **11%**	0.458 11%
Disulfoton	nose only	0.044 4%	0.384 24%	**0.047** **5%**	0.410 28%
Fenamiphos	nose only	0.928 0%	>0.928* 0%	**0.984** **0%**	>0.984* 0%
Fenthion	No inhalation toxicity study was available for fenthion				
Malathion	whole body	115 3%	514 17%	**121** **8%**	540 41%
Methamidophos	head/ nose	0.292 8%	1.432 29%	**0.310** **11%**	1.520 25%
Naled	whole body	0.354 0%	1.594 38%	**0.378** **4%**	1.702 46%
Tetrachlorvinphos	No inhalation toxicity study was available for tetrachlorvinphos.				
Trichlorfon	whole body	9.388 0%	27.44 21%	**3.574** **0%**	9.96 27%

5. Index Chemical (Methamidophos)

The cumulative risk assessment guidance document (USEPA, 2002a) states that the index chemical should be selected based on 1) the availability of high quality dose-response data (preferably in each route of interest) for the common mechanism endpoint ; and 2) that it acts in a toxicologically similar manner to other members of the common mechanism group. High quality dose-response data allows the calculation of PoDs for oral, dermal, and inhalation exposures with confidence intervals. Because the PoD for the index chemical is used to extrapolate risk to the exposure levels anticipated in the human population, any error or uncertainty in an index chemical's PoD value will be carried forward in the cumulative risk estimates. Table I.B-4 lists the PoDs (here, BMD_{10}s) and NOAELs for the oral, dermal, and inhalation routes for methamidophos.

Table I.B-4 Oral, dermal, and inhalation brain BMD_{10}s and $BMDL_{10}$s for Methamidophos, the index chemical.

Route of Administration	Sex	BMD_{10} (mg/kg/day)	BMDL (mg/kg/day)	NOAELs (mg/kg/day)
Oral[a]	F	**0.08** [d]	0.07	0.03*
	M	0.07	0.06	
Dermal[b]	F	**2.12** [d]	1.77	0.75
	M	1.88	1.41	
Inhalation[c]	F	**0.39** [d]	0.21	0.31
	M	0.30	0.20	0.29

[a]MRID nos. 41867201, 43197901, 00148452
[b]MRID no. 44525301
[c]MRID no. 41402401
[d]PoDs for CRA of OPs.

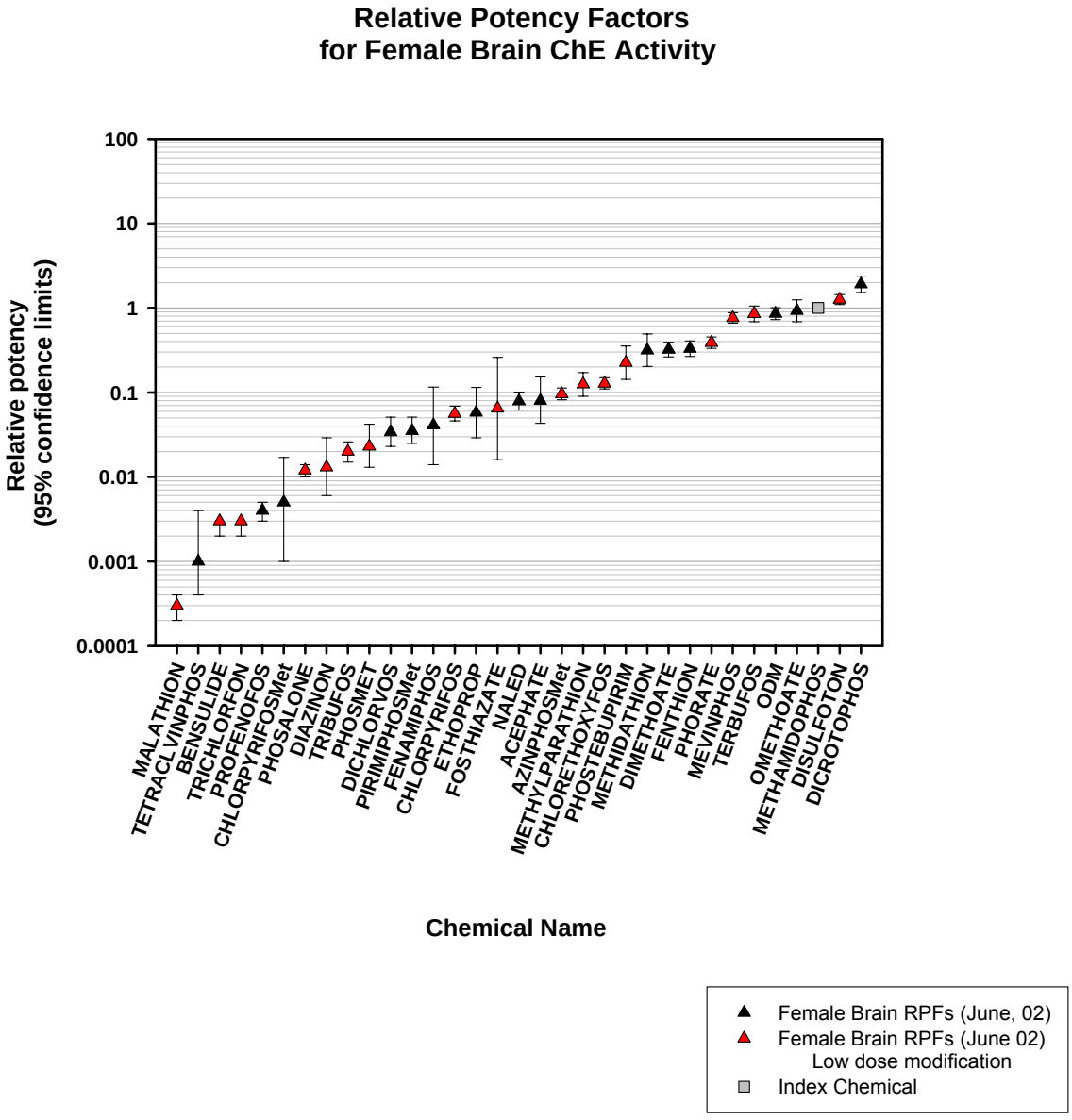
6. Relative Potency Factors for the Cumulative Risk Assessment of the OPs

Table I.B-5 provides the RPFs for the oral, dermal, and inhalation routes of exposure based on brain cholinesterase in female rats which were used in the CRA for OPs. Figure I.B-2 shows the oral RPFs with 95% confidence limits. Although a model-derived oral RPF was determined for fosthiazate, fosthiazate has no appropriate monitoring data to support characterization of exposure from food, and therefore was not included in the quantification of cumulative risk.

Table I.B-5 Relative Potency Factors for Oral, Dermal, and Inhalation routes.

Relative Potency Factors for Female Brain Cholinesterase Activity			
Chemicals	**Oral**	**Dermal**	**Inhalation**
Acephate	0.08	0.0025	0.208
Azinphos-methyl	0.10		
Bensulide	0.003	0.0015	
Chlorethoxyfos	0.13		
Chlorpyrifos	0.06		
Chlorpyrifos-methyl	0.005		
Diazinon	0.01		
DDVP	0.03		0.677
Dicrotophos	1.91		
Dimethoate	0.32		
Disulfoton	1.26	0.47	6.596
Ethoprop	0.06		
Fenamiphos	0.04	1.5	0.315
Fenthion	0.33	0.015	
Fosthiazate	0.07		
Malathion	0.0003	0.015	0.003
Methamidophos	1.00	1.00	1.00
Methidathion	0.32		
Methyl-parathion	0.12		
Mevinphos	0.76		
Naled	0.08	0.075	0.82
Omethoate	0.93		
Oxydemeton-methyl	0.86		
Phorate	0.39		
Phosalone	0.01		
Phosmet	0.02		
Phostebupirim	0.22		
Pirimiphos-methyl	0.04		
Profenofos	0.004		
Terbufos	0.85		
Tetrachlorvinphos	0.001	0.00075	
Tribufos	0.02		
Trichlorfon	0.003	0.0075	0.087

Figure I.B-2 Plot of oral relative potency factors for female rat brain ChE inhibition for the OPs.



7. Uncertainty, Extrapolation, and FQPA 10X Factors

Typically when using data from laboratory animals to extrapolate risk to humans, EPA applies a 10X factor to account for inter-species (animal to human extrapolation). EPA also typically applies a 10X factor for intra-species (i.e., within human extrapolation) variability. These 10X factors are applied as default factors in the absence of specific data to refine them. The FQPA (1996) also mandates that a 10X factor be applied to protect for infants and children unless there are sufficient data to support a different factor of the 10X. The following section provides the assignment and discussion of the inter-species, intra-species and FQPA 10X factors for the OP CRA.

a. Inter-species extrapolation

The adult rat provides the basis for the RPFs and PoDs in the cumulative risk assessment for the OPs[6]. As such, a consideration of interspecies extrapolation from animal to human is necessary. EPA typically applies a 10X factor to account for differences in animals and humans. As discussed previously, the Agency has elected to use data in rats at durations where steady state has been reached. There are studies for some OPs where human subjects were exposed to an acute (single dose) dose. The Agency only considered human studies with repeated dosing for the OP CRA in order to appropriately match the data used to derive the RPFs and PoDs with the data used to refine the inter-species factor. Repeated dosing oral studies with adult, human subjects and measuring blood cholinesterase inhibition are available only for two OPs, azinphos-methyl and DDVP.

In April, 2006, the Agency presented the multi-dosing human studies for azinphos-methyl and DDVP to the Human Studies Review Board (HSRB). As part of the HSRB review, the Agency developed documents called Weight of the Evidence (WOE) papers which describe the strengths and weaknesses of the human studies along with available toxicity and pharmacokinetic information in animals and humans. The HSRB reviewed ethical and scientific aspects of these studies and concurred with the Agency's proposal that neither study was sufficiently robust for evaluating inter-species extrapolation in the CRA of the OPs. The10X factor thus remained for both AZM and DDVP.

[6] The rat provides the basis for the majority of RPFs except for some OPs where rabbit studies were used for some dermal RPFs.

Specifically, in the azinphos-methyl human study, eight subjects were dosed with 0.25 mg/kg/day by capsule for 28 consecutive days and four control subjects were dosed with capsules only. No treatment related effects, including no inhibition of plasma and RBC cholinesterase inhibition, were noted in the treated subjects at the 0.25 mg/kg/day dose level. The HSRB did not support using the azinphos-methyl study primarily as this study includes only one treatment group and is considered a single exposure level- 'NOAEL' study. A single exposure level- 'NOAEL' study is a study whose design includes only one treatment level at which no inhibition of cholinesterase and no adverse events were noted. The HSRB supported previous recommendations of the National Research Council in that 'NOAEL' studies should not be used for risk assessment purposes based, in part, on issues related to statistical power and sample size.

In the DDVP repeated exposure human study, six fasted male volunteers were administered 7 mg of DDVP in corn oil (equivalent to approximately 0.1 mg/kg/day) via capsule daily for 21 days. Three control subjects received corn oil as a placebo. Mean RBC cholinesterase activity was statistically significantly reduced in treated subjects on days 7, 11, 14, 16, and 18 at 8, 10, 14, 14, and 16 percent below the pre-dose mean, respectively. As such, the cholinesterase inhibition was continuing to increase with duration of exposure. Thus, steady state had not yet been achieved in the repeated exposure human study. Because the study was well-conducted, the HSRB supported its use in the single chemical, aggregate risk assessment for DDVP. However, the Board concurred with the Agency's analysis that the repeated exposure human study was not appropriate for use in the OP CRA. This conclusion was based on RBC cholinesterase data that showed that steady state had not been reached in the human subjects. The human data do not appropriately match the RPFs and PoDs derived from steady state measures of cholinesterase inhibition. Thus, the repeated dose human study with DDVP is not appropriate for use in the OP CRA.

In conclusion, the inter-species factor for all OPs, including azinphos-methyl and DDVP, in the CRA is the standard 10X factor.

b. Intra-species extrapolation

The Agency typically applies a standard 10X factor for intra-species extrapolation (i.e., variation in sensitivity among the members of the human population) unless there is sufficient data to inform a different value. In the past few years, there has been a significant amount of research directed at human variability and polymorphisms regarding PON1, including a recent study by Furlong et al. (2006). PON1 (paraoxonase 1/arylesterase) is an enzyme that has been shown to detoxify chlorpyrifos oxon, paraoxon, and diazoxon (Davies et al., 1996). Research has demonstrated a large range of variability in the human population for PON1 that can exceed 10X (Furlong et al., 2005; Costa et al., 2005). Specifically, Davies et al. (1996) have reported up to 13-fold variation in PON1 levels in adults. More recently, Furlong et al. (2006) predicted a range in sensitivity to diazoxon up to 26-fold and 14-fold in a group of newborns and Latino mothers, respectively.

Interpreting the variability in enzyme levels in the context of increased sensitivity to OPs needs to be done cautiously. Timchalk et al. (2002) used a physiologically-based pharmacokinetic model (PBPK) model for chlorpyrifos to evaluate the impact of variability associated with chlorpyrifos-oxonase polymorphisms on the theoretical concentrations of chlorpyrifos -oxon in the human brain over a range of chlorpyrifos doses. The authors reported that over a range of dose-levels, the response was relatively insensitive to changes in oxonase activity at low doses. However, chlorpyrifos-oxonase status may be an important determinant of sensitivity with increasing dose. The authors further suggest that other esterase detoxification pathways may adequately compensate for lower chlorpyrifos-oxonase activity; hence an increased sensitivity to low chlorpyrifos-oxonase is not observable until other detoxification pathways or esterases have been appreciably depleted or overwhelmed.

The simulations performed by Timchalk et al. (2002) point to the complicated nature of OP metabolism and sensitivity and the need for further research into the metabolic processes and genetic factors which influence sensitivity to OPs. For risk assessment purposes, human responses at low, environmental levels are the most relevant. Moreover, the majority of studies on the PON1 enzyme have focused on chlorpyrifos, diazinon, and parathion. Parathion has been cancelled in the US. The residential uses of diazinon and chlorpyrifos have been heavily mitigated in recent years. As such, there are no

data on most of the OPs to further inform the intra-species extrapolation factor.

At this time, there is not sufficient information to refine the intra-species factor for the CRA. Furthermore, the Agency believes that the standard 10-factor for intra-species extrapolation in conjuction with 10X interspecies factor as well as the FQPA 10X safety factor incorporated in many RPFs is protective of human health for the OP CRA.

In conclusion, the standard 10-factor for intra-species extrapolation has been applied to the OP CRA

c. FQPA 10X Factor

i. Background

The FQPA (1996) instructs EPA, in making its "reasonable certainty of no harm" finding, that in "the case of threshold effects, **an additional tenfold margin of safety** for the pesticide chemical residue and other sources of exposure shall be applied for infants and children to take into account **potential pre- and postnatal toxicity and completeness of data with respect to exposure and toxicity to infants and children**." Section 408 (b)(2)(C) further states that "the Administrator may use a different margin of safety for the pesticide chemical residue only if, on the basis of reliable data, such margin will be safe for infants and children."

The FQPA requires that the Agency consider issues related to toxicity and exposure. The text contained in this chapter only considers potential sensitivity of infants and children with respect to toxicity. The risk characterization (I.G) chapter contains a more complete discussion of issues related to exposures from food, water, and in/around the home that could contribute to increased exposure to infants and children relative to adults. However, the Agency believes that there are quality data and scientifically supportable methods to account for specific exposure and behavioral patterns of children. Because characteristics of children are directly accounted for in the exposure assessment and the Agency's methods are not expected to underestimate exposure to OPs, evaluating the potential for increased toxicity of juveniles is the key component in determining the magnitude of the FQPA factors in the CRA.

As described in detail in OPP's cumulative risk assessment guidance, determination of relative toxic potency should be calculated using a uniform basis of comparison, by using, to the extent possible, a common response derived from the comparable

measurement methodology, species, and sex for all the exposure routes of interest (USEPA 2001a, 2002a). For the OPs, estimates of relative potency are required for more than 30 pesticides. Toxicology studies in the adult rat provided the most extensive cholinesterase activity data for all routes, compartments, and both sexes and as a result provide the basis for the RPFs and PoDs in the CRA. Since adult rat data has been used to derive the RPFs and PoDs, EPA has retained the 10X FQPA Safety Factor unless reliable data are available addressing the sensitivity of the young such that EPA can determine that a different safety factor value is protective of infants and children.

Consistent with the mode of action for OPs (ie, neurotoxicity mediated through the inhibition of acetycholinesterase), two critical studies—the development neurotoxicity study (DNT) and the comparative cholinesterase study in juvenile and adults—provide the most relevant data for evaluating potential sensitivity to infants and children to OPs. For a number of OPs, DNTs and comparative ChE data are available and can be used to derive a chemical-specific factor for use in the cumulative risk assessment to reflect the differential sensitivity of children and infants compared to adults. For other OPs without such data, the 10X Safety Factor is retained. As described in detail below, the Agency has focused the current analysis on a subset of OPs which were identified as potential non-negligible contributors to the cumulative risk assessment. For these OPs, the results of the comparative ChE are more sensitive than results of the DNT. In others words, for these OPs, cholinesterase inhibition is a more sensitive endpoint than functional or behavioral effects identified in the DNT. Because the comparative ChE studies provide sensitive results, the data provided from these studies have been judged as reliable and identified for use in the cumulative risk assessment as the most appropriate studies for developing the chemical-specific factors to address the potential susceptibility of infants and children to the effects of OP exposure.

As described in detail below, the Agency has used a dose response modeling approach for evaluating quantitatively the relative sensitivity between juvenile and adult rats. In this approach, a BMD was calculated for juvenile and adult brain ChE data. The ratio of the juvenile and adult BMDs was calculated—this ratio has been used mathematically as the data-derived, chemical-specific FQPA safety factory. This approach is different from, but not inconsistent with, approaches used in the single chemical aggregate risk assessments. In single chemical aggregate risk assessments, the mathematical calculations are more simple and straightforward as only one active ingredient in included. As such, in single chemical risk assessments,

when available, data from young or juvenile can be (and has been) used directly as the PoD. When the data are from the young are considered directly in deriving a PoD and the PoD is set based on that data or data showing more sensitive effects, the FQPA Safety Factor can be reduced or removed so long as there are no residual concerns regarding potential pre- and post-natal toxicity or concerns regarding the completeness of the toxicity or exposure databases. In the 2006 Updated CRA, the data-derived FQPA factor is used to adjust the chemical specific RPF to account for the potential increased sensitivity of the young.

In June, 2002, the Agency presented its preliminary analysis of the potential sensitivity of infants and children to OPs and proposed FQPA 10X factors to the FIFRA SAP. Following the comments of the public and the SAP, the Agency has revised its FQPA 10X analysis. The Agency's preliminary analysis contains a substantial literature review of issues related to the role of acetylcholinesterase in neurodevelopment, pharmacokinetic differences in adults and children, recovery of young rats following high doses of OPs, and biomonitoring of children's exposure to OPs. This literature review is not repeated here. In addition, the preliminary analysis described data from studies in many OPs that showed that following *in utero* exposure to OPs, dams exhibit larger amounts of ChE inhibition compared to fetuses. Appendix II.B.2 expands the preliminary analysis to include RBC and brain cholinesterase data from gestational dosing with a subset of OPs that further support the conclusion that dams exhibit more inhibition than fetuses during pre-natal exposure. As such, for purposes of risk assessment, data from post-natal exposures in juvenile and adult rats provide the most robust toxicity data for determining the magnitude of the FQPA factor for the OP CRA.

In the updated analysis, the Agency has relied primarily on comparative cholinesterase studies in juvenile and adult animals to evaluate the potential sensitivity of young animals to cholinesterase inhibition. Brain cholinesterase inhibition is the focus of this analysis as brain cholinesterase inhibition has been selected as endpoint for derivation for RPFs and PoDs in the OP CRA. Comparative cholinesterase studies can involve acute or repeated dosing to adult and juvenile rats. To best match the duration of exposure used to derive RPFs and PoDs, for the OP CRA, the Agency has considered the *repeated dosing exposure* studies only. In this analysis, the Agency has not proposed a FQPA safety factor for the entire common mechanism group as was done in the preliminary analysis. Instead, the Agency has evaluated each OP individually.

ii. Approach

In accordance with the FQPA (1996), the Agency began its analysis by assigning each OP a FQPA factor of 10X. Next, the Agency used a screening-level approach to identify a subset of OPs considered to be potential contributors to the cumulative risk either from food, water, or residential pathways. Specifically, the chemicals selected for the refined FQPA analysis were selected from those chemicals identified in the revised CRA (USEPA, 2002) as OPs that may be non-negligible contributors to the cumulative risk from food, water, or residential pathways. In addition, those OPs whose chemical structure and/or physical –chemical properties suggested that they may form oxons or sulfone/sulfoxide oxons during the drinking water treatment process were also included in the refined FQPA analysis (See Drinking water chapter). Fosthiazate, a recently registered OP, was also included. For the remaining OPs, a FQPA factor of 10X was retained.

Following this screening approach, the Agency searched the scientific literature and pesticide registration databases for toxicity studies which measured brain cholinesterase inhibition in juvenile and adult rats following repeated dosing. For all the OPs except chlorpyrifos, a BMD analysis was then performed on the brain cholinesterase data in juvenile and adult animals extracted from comparative cholinesterase studies. For those OPs who were identified as potential contributors to risk without comparative ChE data in juvenile and adult rats, a FQPA factor of 10X was retained. Thus, the Agency's refined FQPA analysis focused on 13 OPs[7] which were identified during the screening approach and which had a repeated dosing, comparative cholinesterase study. For all other OPs, a FQPA factor of 10X was retained.

The BMD analysis of cholinesterase data from the OP oral gavage, repeated, comparative sensitivity toxicity studies was performed using EPA's OPCumRisk program. The exponential function used for modeling the effect of OP on cholinesterase activity was:

$$y = B + (A - B)\, e^{-m \times dose}$$

Where **y** is ChE activity, **dose** is the dose in mg/kg, **m** is the dose scale factor, **A** is background cholinesterase activity, and **B** is the limiting high-dose cholinesterase activity. Both y (cholinesterase activity) and dose were extracted from the above referenced toxicity

[7] The results of the analysis for dimethoate have been applied to direct exposures to omethoate, the oxon metabolite of dimethoate.

study. The equation for the exponential model reflects the observation that cholinesterase activity decreases to a limiting value (B) as dose increases. The model has three parameters to be estimated: m (dose scale factor), A (background), and B (limiting high-dose cholinesterase activity).

The OPCumRisk program utilizes the same dose-response model (i.e., decreasing exponential model) as utilized in the Preliminary OP Cumulative Risk Assessment (CRA; USEPA, 2001). The OPCumRisk program can be obtained at www.epa.gov/pesticides/cumulative/EPA_approach_methods.htm. These dose-response models and the respective computer code are publicly available for download, review, and use. This method has been previously evaluated by the FIFRA SAP (www.epa.gov/scipoly/sap/2001/index.htm). For the revised OP CRA (USEPA, 2002), the exponential model was expanded to include a "low dose shoulder." The low dose shoulder corresponds to the portion of the dose-response curve where the slope at the low end of the dose-response curve is flatter compared to the slope at higher doses. This low dose shoulder is not modeled in the OPCumRisk program. For azinphos-methyl, the Agency performed a more refined BMD analysis using the expanded model to account for the low dose shoulder. Specific details for the azinphos-methyl analysis can be found in Appendix II.B.1. Cholinesterase data used in the BMD analyses of the repeated dosing comparative cholinesterase studies are provided in Appendix II.B.4.

For each cholinesterase dataset, parameters were initially estimated including all dose groups. The OPCumRisk program utilizes a decision algorithm for selecting from among various options for the exponential model. Generally the model is fitted until an adequate p-value for the $\chi 2$ goodness-of-fit (GoF) statistic is obtained. The decision algorithm is provided below.

1. If the p-value for the GoF statistic is greater than 0.05, then the model's fit was considered adequate and the initial parameter estimates were used.

2. Otherwise (that is, if the p-value was less than 0.05, or no estimates resulted because the model did not converge), the horizontal asymptote was set to zero and the model was refit to the data.

3. If the p-value was still less than 0.05, or there was no model fit at all, then the highest dose was dropped and the model was

refit with the horizontal asymptote set to zero until either the p-value exceeded 0.05, or there were only three doses remaining.

Although the user can specify options that are not consistent with the default decision algorithm utilized by OPCumRisk, all BMD values provided in these analyses are based on the default decision algorithm. The decision algorithm and technical details of the "basic" exponential model used in this BMD analysis can be obtained at www.epa.gov/scipoly/sap/2001/september/rpfappendix1.pdf

The results of the BMD analysis are provided in Table I.B 6 below. For acephate, dimethoate, disulfoton, dicrotophos, DDVP, fosthiazate, methamidophos, and terbufos, the simple BMD analysis provided a reasonable fit to the female brain cholinesterase data. For these eight OPs, the ratio of the BMD_{10}s for brain cholinesterase inhibition was calculated for male and female adults and pups (i.e., adult BMD_{10}/pup BMD_{10}). The ratio for the more sensitive sex was selected as the FQPA factor (Table I.B-7).

The simple model did not provide adequate fit for azinphos-methyl and diazinon. For diazinon, the BMD estimates were highly variable among the sexes and age groups. No further refinements to the diazinon FQPA factor were performed; a 10X factor was retained for diazinon. For azinphos-methyl female data only, the Agency performed the expanded analysis to account for a low dose shoulder in the data. In the azinphos-methyl study, male and female pups responded similarly but the adult females showed more inhibition at the highest dose than the male adults. Thus, the Agency focused its refined expanded analysis on the more sensitive sex (i.e., females).

For methyl parathion, the pup data were modeled well with the basic model but the adult data were not. For methyl parathion, the 10X factor was retained. In the phorate study, there was no dose related inhibition of brain ChE in pups or adults at all doses and thus it is not possible evaluate potential age-related sensitivity; the 10X factor was retained.

Regarding chlorpyrifos, the Agency has not performed a BMD analysis but has generated a plot of the data from Zheng et al (2000). Dr. Carey Pope of Oklahoma State University provided the data in Figure I.B-3 to the Agency. The estimated dose to result in 10% brain ChE inhibition is noted as the dotted line in the graph. At this dose, there is no difference in response between pups and adult rats. Thus, the FQPA factor for chlorpyrifos in the OP CRA for repeated exposures is 1X.

In the summary, the Agency has retained the 10X factor for most of the OPs in the CRA. The Agency has refined this factor for 10 OPs (and omethoate) that were identified as potential contributors to the cumulative risk and had high quality repeated dose comparative ChE data in young and adult animals.

Figure I.B-3 Plot of chlorpyrifos data from Zheng et al (2000).

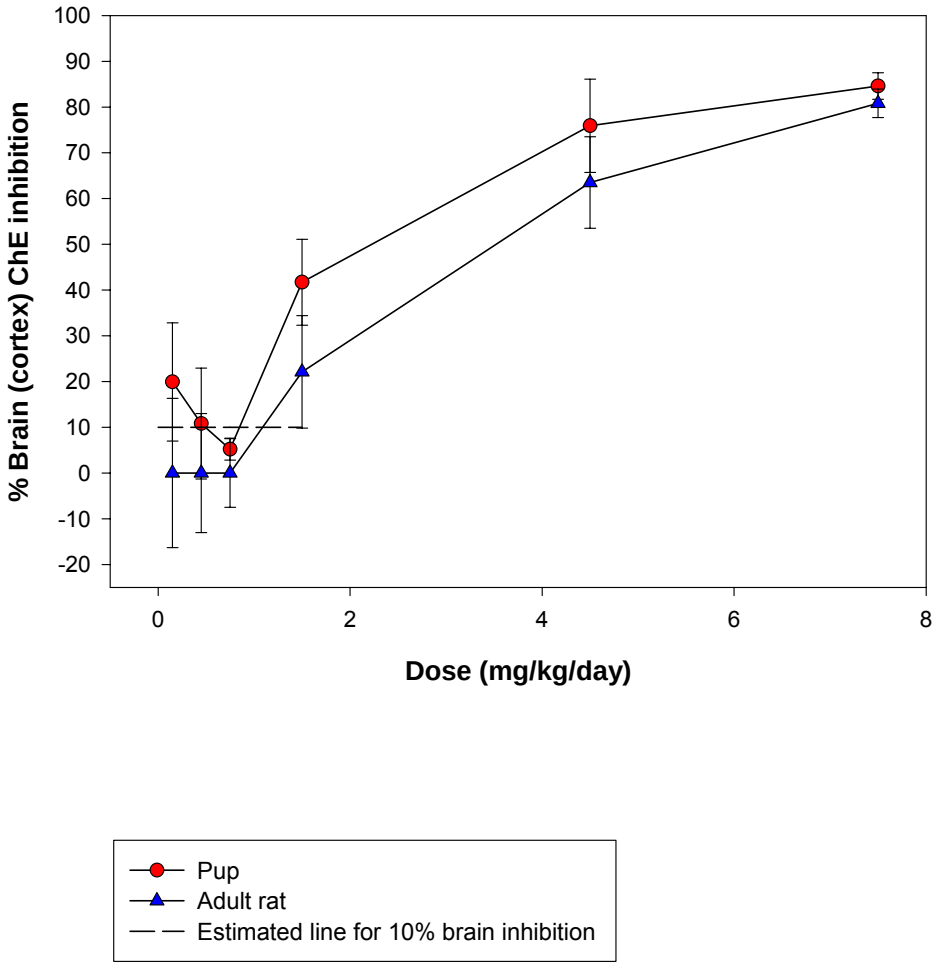


Table I.B-6 Summary of BMD_{10}s and $BMDL_{10}$s from comparative cholinesterase studies (repeated dosing only) in juvenile and adult rats for selected OPs.

OP	Gender	Age	BMD	BMDL	P Value	Comment
Acephate	Male	Adult	0.27	0.22	0.02	Quality fit
		Pup	0.42	0.30	0.47	
	Female	Adult	1.25	0.73	0.10	
		Pup	1.13	0.60	0.59	
Azinphos methyl	Female	Adult	1.14	1.04	expanded model used for female data only	Quality fit
		Pup	0.25	0.22		
Diazinon	Male	Adult	40.57	27.87	0.54	Poor fit of pup data; 10X retained.
		Pup	1.08	1.00	1.35E-06	
	Female	Adult	0.39	0.29	0.65	
		Pup	0.72	0.68	0.008	
Dicrotophos	Male	Adult	0.11	0.09	0.23	Adequate fit for adults, Quality fit for pups
		Pup	0.06	0.05	0.47	
	Female	Adult	0.09	0.07	0.020	
		Pup	0.05	0.04	0.79	

OP	Gender	Age	BMD	BMDL	P Value	Comment
Dimethoate	Male	Adult	0.48	0.22	0.87	Quality fit
		Pup	0.39	0.29	0.59	
	Female	Adult	0.37	0.34	0.7	
		Pup	0.41	0.26	0.81	
Disulfoton	Male	Adult	0.11	0.09	0.11	Quality fit
		Pup	0.05	0.05	0.02	
	Female	Adult	0.07	0.06	0.04	
		Pup	0.05	0.04	0.06	
DDVP	Male	Adult	0.72	0.55	0.71	Quality fit
		Pup	0.88	0.75	0.008	
	Female	Adult	0.88	0.71	0.84	
		Pup	0.95	0.8	0.02	
Fosthiazate	Male	Adult	1.89	1.65	0.16	Quality fit
		Pup	0.74	0.59	0.90	
	Female	Adult	0.60	0.55	0.14	
		Pup	0.48	0.44	0.28	
Methamidophos	Male	Adult	0.10	0.08	0.11	Quality fit
		Pup	0.08	0.06	0.55	
	Female	Adult	0.18	0.11	0.09	
		Pup	0.09	0.08	0.96	

OP	Gender	Age	BMD	BMDL	P Value	Comment
Methyl Parathion	Male	Adult	Poor fit			Poor fit of adult data; 10X retained
		Pup	0.09	0.07	0.15	
	Female	Adult	0.66	0.50	0.0002	
		Pup	0.11	0.09	0.81	
Phorate	Male	Adult	Poor dose response data			10X retained
		Pup				
	Female	Adult				
		Pup				
Terbufos	Male	Adult	0.10	0.04	0.43	Quality fit
		Pup	0.02	0.01	0.57	
	Female	Adult	0.02	0.008	0.56	
		Pup	0.02	0.01	0.18	

Table I.B-7 FQPA 10X factors for OPs in the Cumulative Risk Assessment.

OP	FQPA 10X Factor
Acephate[a]	**1**
Azinphos-methyl	**4.5**
Bensulide	10
Chlorethoxyfos	10
Chlorpyrifos	**1**
Chlorpyrifos methyl	10
Diazinon	10
DDVP	**1**
Dicrotophos	**1.7**
Dimethoate	**1**
Disulfoton	**2.2**
Ethoprop	10
Fenamiphos	10
Fenthion	10
Fosthizate	**2.6**
Malathion	10
Methamidophos	**2**
Methidathion	10
Methyl Parathion	10
Mevinphos	10
Naled	10
ODM	10
Omethoate[b]	**1**
Phorate	10
Phosalone	10
Phosmet	10
Phostebupirim	10
Pirimiphos methyl	10
Profenofos	10
Terbufos	**6.5**
Tetrachlorvinphos	10
Tribufos	10
Trichlorfon	10

a. Chemicals in bold have refined FQPA factors
b. Oxon metabolite of dimethoate

8. Incorporation of Uncertainty/Extrapolation Factors and the Target Margin of Exposure

In general, when performing a cumulative risk assessment using a RPF approach, like that done for the OPs, uncertainty and extrapolation factors can be incorporated into the risk assessment in two different ways: 1) adjustment of the chemical-specific RPF or 2) incorporation into the target Margin of Exposure.

Adjustment of the Chemical-Specific RPF. In cases where the uncertainty or extrapolation factor varies among the chemicals, the chemical-specific RPF is adjusted (i.e., multiplied) by the uncertainty or extrapolation factor. In the case of the OPs, the FQPA factor varies among the chemicals. As such, the Agency has multiplied the RPFs reported in Table I.B 5 by the FQPA factors reported in Table I.B-7 to generate FQPA-adjusted RPFs. In this way, the RPFs are directly adjusted by the chemical-specific FQPA factors.

Incorporation into the Target Margin of Exposure (MOE). There may be assessments where the magnitude of an uncertainty or extrapolation factor is the *same* for each member of the common mechanism group. In these assessments, the target MOE identified addresses the total magnitude of the uncertainty or extrapolation factor(s). This is the situation for the intra- and inter-species extrapolation factors in the OP CRA where the standard 10-fold factors have been applied. Ten-fold factors for inter- and intra-species are multiplied to generate a total of 100. As such, the target MOE for the OP CRA is 100 accounting for inter- and intra-species extrapolation.

9. Oxons

Many OPs are active cholinesterase inhibitors as the parent active ingredient. Many other OPs, however, require activation to the oxon metabolite. Based on *in vivo* data from laboratory animals administered oxons directly, oxons are more potent than the parent OP. Under some conditions, oxon metabolites may be formed in the environment. The food, residential, and drinking water exposure assessments in the OP CRA have each considered the potential for direct oxon exposure. A tiered approach was taken to evaluate the risk to the oxon forming OPs. First, the Agency evaluated the extent to which monitoring or laboratory studies supported the potential formation of oxons in the environment. From this analysis, the Agency concluded that with the exception of dimethoate/omethoate, residues of oxon degradates are extremely low or negligible in food. Regarding residential exposure, limited information is also available to indicate that three of the OP pesticides with

residential uses may also degrade to oxons. In order to evaluate the potential effects of these transformations on the OP CRA, OPP has conducted a number of sensitivity analyses. Based on the sensitivity analyses conducted for oxon exposure through the residential pathways, OPP concludes the potential for formation of oxons will not substantially alter the risk estimates provided in this assessment. Regarding drinking water exposure, formation of oxons, oxon-sulfone, and/or oxon-sulfoxide can occur from drinking water treatment processes However, as described in I.E, some oxon-sulfone and oxon-sulfoxide degradates are not stable. Table I.B-8 provides a list of currently registered OPs that may under some conditions form oxons in the environment[8].

Regarding the toxic potency of oxon chemicals, omethoate has its own RPF calculated using BMD techniques. For methyl parathion and chlorpyrifos, data from Chambers and Carr (1993) indicate that the potency of methyl paraoxon and chlorpyrifos-oxon are expected to be within 10-fold of the parent OP. No *in vivo* toxicity data were available for the remaining oxons. For purposes of the screening assessment, other oxons were assumed to be 10X and 100X more potent than the parent OP. Appendix II.G.2 describes the impact of the 10X and 100X oxon factors on the cumulative risk, particularly in drinking water.

[8] OPs not included in this table do not require activation to form the oxon; may be cancelled or undergoing phase out; have use patterns which do not support potential oxon formation; or have laboratory/monitoring data that do not indicate potential exposure in the environment. Direct exposure to malaoxon and a toxicity adjustment factor for malaoxon were included in the Malathion RED. Because malathion is not a significant contributor to the cumulative risk assessment, refinements for malathion were not performed here.

Table I.B-8 OPs that may form oxons and toxicity information to inform their potency.

OP	Oxon
Bensulide	No data to inform 10x and 100x to characterize the oxon
Chlorethoxyfos	No data to inform 10x and 100x to characterize the oxon
Chlorpyrifos	Oxon <10X compared to parent (Chambers and Carr, 1993)
Diazinon	No data to inform 10x and 100x to characterize the oxon
Dimethoate	Omethoate RPF available
Disulfoton	No data to inform 10x and 100x to characterize the sulfone oxon
Malathion	10x and 100x to characterize the oxon. Steady state data are available for malaoxon[9]. Malathion is not a significant contributor to the CRA; refinement for brain ChE inhibition from malaoxon not necessary.
Methidathion	No data to inform 10x and 100x to characterize the oxon
Methyl parathion	Oxon <10X compared to parent (Chambers and Carr, 1993)
Phostebupirim	No data to inform 10x and 100x to characterize the oxon

[9] A oxon adjustment factor of 61 was used in the malathion RED to account for direct exposures for malaoxon. The value of 61 was derived from steady state RBC ChE inhibition data in adult rats.

10. Summary

The Hazard Characterization for the Cumulative Risk Assessment of the OPs is contained in Section I.G.

This chapter has described the application of the RPF method in the cumulative hazard assessment for the OPs. Whole brain ChE from female rats is a sensitive, health protective endpoint representing the target tissue. The brain data provide the most appropriate dataset for extrapolating cumulative risk to this common mechanism group. Potency for the OPs varies over several orders of magnitude. Methamidophos has been selected as the index chemical because of its high quality animal ChE data from oral, dermal, and inhalation exposure. The Agency considered the available toxicity studies with human subjects and has determined that none are appropriate for use in informing the inter-species extrapolation factor for the CRA. The Agency established chemical-specific FQPA factors. For most OPs, a 10X FQPA factor was assigned. For select OPs with high quality brain ChE data in pups and adult rats, the FQPA factors were refined. Since the FQPA factors for each OP are used to adjust the RPFs for each chemical, the target MOE for the CRA is 100 to account for inter- and intra-species extrapolation.

C. Cumulative Risk from Pesticides in Food

In June 2002, the EPA released its Revised OP Chemicals Cumulative Risk Assessment (OP CRA), which included the cumulative dietary risk due to the use of Organophosphorus Pesticides on food crops. The current chapter emphasizes changes, modifications, and updates to the 2002 Revised OP CRA based on the most current available information, and thus provides only a brief introduction to the background and to some of the more detailed technical issues and methods which are described more fully in the 2002 document. This chapter is designed to be read in conjunction with the corresponding chapter concerning cumulative risk from foods in the Revised OP CRA. The reader is encouraged to review this 2002 document (available at http://www.epa.gov/pesticides/cumulative/rra-op/) for additional details and background material.

1. Introduction to Food

As described in the 2002 Revised OP CRA, the cumulative dietary risk associated with the use of OP Pesticides on food crops was assessed using residue monitoring data collected by the United States Department of Agriculture's (USDA) Pesticide Data Program (PDP) and dietary consumption data collected by USDA's Continuing Survey of Food Intakes by Individuals (CSFII). The BMD10 for brain cholinesterase inhibition in female rats was chosen as the toxicological PoD for this assessment. Methamidophos served as the index chemical. The residue values for the other OP pesticides were converted to methamidophos equivalents using an RPF approach. The 2002 Revised OP CRA included residue data collected on approximately 44 food commodities monitored by PDP between the years of 1994 and 2001. This supplement updates the 2002 Revised Assessment to include the 2002-2004 PDP data, which includes ten food commodities (applesauce, asparagus, barley, beef muscle, beef adipose, beef liver, cauliflower, mushroom, onion, and pear juice) not previously monitored by PDP. Food processing factors were applied to specific pesticide-commodity pairs to extend these data for use on cooked and processed food/food forms in the analysis. The food processing factors used here in this update are unchanged from the Revised OP CRA as no additional data are available to EPA. The PDP residue data were further extended to other commodities identified as reasonable for translation of pesticide residue data per OPP/HED SOP 99.3 (USEPA, 1999b); see Appendix II.C.4 for these details.

The residue data were compiled as distributions of cumulative residues of methamidophos (index chemical) equivalents and, after application of processing factors and FQPA factors, were summed on a

sample-by-sample basis. These residue distributions were combined with a distribution of daily food consumption values via a probabilistic procedure to produce a distribution of potential exposures for several age groups in the CSFII 1994-1998 (Infants < 1, children 1-2, children 3-5, children 6-12, youths 13-19, adults 20-49, adults 50+ years old, and females 13-49 years old). The most highly exposed age groups were again confirmed to be children 1-2 and children 3-5 years old.

2. Source of Pesticide Residue Data

a. USDA-PDP

As with the 2002 Revised OP CRA, this update also relies primarily on the PDP program for residue data. The PDP program has been collecting pesticide residue data since 1991, primarily for purposes of estimating dietary exposure. The program focuses on high-consumption foods for children and reflects foods typically available throughout the year. Foods are rinsed and the inedible portions (e.g, orange peels and apple cores) are removed before analysis. This 2006 update adds PDP data collected in 2002-2004 to the 1994-2001 data used in the 2002 Revised Assessment. A complete description of the PDP program and all data through 2004 are available online (http://www.ams.usda.gov/science/pdp). The PDP residue data on OP chemicals included in this update are summarized in Appendix II.C.2. Appendix II.C.1 lists all of the foods for which estimated residues were based on PDP data.

b. MBS of OP Residues in Applesauce

The Apple Processors Association (APA) sponsored a market basket study (MBS) of OP pesticide residues in applesauce samples collected in 1999. These data were incorporated in the 2002 OP cumulative assessment for applesauce and baby food applesauce. PDP included applesauce as part of its 2002 sampling program and, for this update, the more current PDP applesauce data replaced the applesauce data collected by the APA. The distributions of residues for the two surveys are similar[10].

c. FDA-CFSAN Surveillance Monitoring Data

The Food and Drug Administration's (FDA's) Center for Food Safety and Applied Nutrition (CFSAN) Surveillance Monitoring Program is designed primarily for enforcement of EPA pesticide

[10] As described more fully in Section I.A.2.d.i of this update, the Agency will be phasing out domestic uses of azinphos-methyl on apples. As such, the 2002 PDP data for applesauce were adjusted to incorporate this effect (i.e., residues of AZM on apples were removed).

tolerances on imported foods and domestic foods shipped in interstate commerce. In this monitoring program, domestic samples are generally collected close to the point of production in the distribution system. Import samples are collected at the point of entry into US commerce. The emphasis in sample collection is on the agricultural commodity, which is analyzed as the unwashed, whole (unpeeled), raw commodity. Processed foods are also included in the program. A description of the program and residue data for recent years can be found online at http://vm.cfsan.fda.gov/~lrd/pestadd.html. Because the emphasis of this program is not on dietary exposure, it is being used in the current assessment mostly as a semi-quantitative check on the potential for residues and as support for data from other sources. The program has extensive data available on eggs and fish, which support the judgment that OP residues are negligible on these foods as consumed. Thus, in the OP CRA Update 2006, OP residues on eggs and fish were assigned residue values of zero. Appendix II.C.1 indicates the foods for which exposure estimates were supported by this program.

d. FDA-CFSAN Total Diet Study

The FDA's CFSAN Total Diet Study (TDS) has provided data on dietary intake of food contaminants for about 45 years. A program description and residue data can be found at the same Internet site listed above for FDA Surveillance Monitoring Data. Foods are purchased in grocery stores, generally 3 or 4 times a year, prepared and cooked for consumption, and analyzed by highly sensitive multi-residue methods. Between 1991 and 2003, there have been 44 market baskets collected and approximately 260 foods analyzed for -- among other things -- OP pesticide contamination. A disadvantage of these data is that only one sample of each food is analyzed in each market basket. For this reason, these data have been used primarily as semi-quantitative support for judgments on residues in foods.

Previously – in the revised OP CRA -- conservative estimates of OP residue values for some highly consumed foods such as beef were based on the TDS data. Beef, poultry, and pork have now entered the PDP program. PDP data on beef replaces the corresponding FDA TDS data used in the 2002 Revised OP CRA. Both surveys support the previous understanding that beef, poultry, and pork are negligible contributors to dietary exposures to the OP pesticides

3. OP Pesticides Included in the Food Risk Assessment

All of the OP analytes detected in the PDP program for which no mitigation actions (e.g. tolerance revocation) have been taken are included in the current assessment. See Appendix II.C.2 for a complete

summary of the laboratory analyses for OP pesticides and metabolites on each food commodity in the database. There have been significant numbers of analyses for 64 OP active ingredients, degradates, or metabolites between 1994 and 2004. A total of 39 of these OP analytes have been detected in at least one of the foods analyzed. After excluding data on pesticides that have been cancelled[11] or do not have food uses, and combining data for metabolites and degradates, analytical data are being used for 25 OP pesticides, as follows:

acephate	azinphos-methyl[12]	chlorethoxyfos
chlorpyrifos	chlorpyrifos methyl	diazinon
DDVP	dimethoate	disulfoton
ethoprop	fosthiazate	malathion
methamidophos	methidathion	methyl-parathion
mevinphos[11]	oxydemeton-methyl	phorate
phosalone	phosmet	pirimiphos-methyl
profenofos	terbuphos	tetrachlorvinphos
tribufos		

With exception of chlorethoxyfos, profenophos and tetrachlorvinphos, the following pesticides have not been included in this 2006 update to the OP cumulative assessment.

- Naled has generally not been separately analyzed by PDP and residues from this use would be appropriately reflected in the DDVP analyses to which it degrades.

- Bensulide is not included in the PDP data; however, negligible residues would be expected in foods based on field trial data submitted for registration purposes.

- Cadusafos was analyzed by PDP in 2001 through 2003 on various commodities. The only registered use that could potentially result in food residues is as a nematacide soil application on imported bananas. Field trial data submitted for registration/tolerances purposes indicate

[11] However, data from samples that had violative residues in PDP were retained.

[12] Domestic uses of mevinphos have been cancelled. However the tolerances for this chemical have not been revoked, allowing for use on imported commodity to remain. The dietary assessment still includes PDP data on imported samples for mevinphos.

In June 2006, the Agency issued its proposed decision to phase-out all remaining uses of AZM. Some uses are scheduled to be phased-out by 2007, and the remaining uses are scheduled to be phased-out by 2010. The Agency has evaluated OP cumulative risks two ways – with the remaining AZM uses included and with the remaining uses excluded. The OP Cumulative Assessment (2006 Update) reflects the termination of these uses, but also contains discussion about the results if the AZM uses are included in the assessment. Additional information and background is available in Section I.A and in Section I.G of this update.

that residues will not occur in the edible portion of the banana. The PDP analyses confirm that there are no detectable residues of cadusafos in bananas or other commodities.

- Chlorethoxyfos was analyzed by PDP in 2001 through 2004 on various commodities. Chlorethoxyfos was not included in the previous assessment, but was included in this revision. The only registered food use is soil application to corn crops at a low rate; therefore, significant residues in edible portions and processed foods from corn would not be expected. The PDP analyses confirm that there are no detectable residues of chlorethoxyfos in sweet corn or other commodities.

- Dicrotophos, not included in PDP food data, has one food use on cotton. Cottonseed oil is the only food commodity of cotton and it is not included in the current assessment, but the impact of the chemical on dietary (food) exposure is expected to be low due to the extent of refining and blending of the oil.

- Tebupirimphos (phostebupirim) has one food use on corn, mainly to control root worm. Significant contribution to cumulative food exposure is not expected since residues in edible portions and processed foods from corn would not be expected. PDP data on tebupirimphos consists of limited drinking water samples.

- Profenofos is used on cotton and various animal commodities. Profenofos was not included in the previous assessment, but was included in this revision. No detectable residues of profenofos were found in any of the commodities analyzed by PDP including animal commodities. Although PDP has not analyzed cotton or cotton seed oil, the impact of the chemical on dietary exposure is expected to be low due to the extent of refining and blending of the oil.

- Trichlorfon has no food uses except for an overseas use as pour-on treatment of beef cattle. PDP does not analyze for trichlorfon. However PDP does test for the trichlorfon degradate, DDVP. No detectable residues of DDVP have been found in any PDP beef samples.

- Tetrachlorvinphos is used only in livestock feed to control fecal flies. Tetrachlorvinphos was not included in the previous assessment, but was included in this revision. The only detectable residue of tetrachlorvinphos was found in one PDP carrot sample in 2001. Although tetrachlorvinphos is not registered on carrots, the sample was included in the assessment. No other detectable residues were found in any of the other commodities analyzed by PDP including animal commodities.

- Fenthion has not been included since all uses are scheduled to be cancelled.

- Fenamiphos has not been included since all uses are scheduled to be cancelled.

4. Foods Included in the Food Risk Assessment

The universe of foods included in the cumulative dietary exposure assessment is defined by the USDA CSFII for the years 1994-1996 with supplementary data on children obtained in 1998. The survey data, CSFII 1994-1996/1998, is integrated into the dietary exposure software used in this assessment, Dietary Exposure Evaluation Model (DEEM™). The version of DEEM™ employed by the Agency incorporates food translations from the EPA/USDA Food Commodity Intake Database (FCID) and is commonly referred to as DEEM-FCID™. Appendix II.C.1 lists all of the foods in CSFII 1994-1998 in decreasing order of their relative per capita consumption by children 1-2 years old and children 3-5 years old.[13]

Appendix II.C.7 contains a complete listing of the food forms in the DEEM-FCID™ software that were included in this assessment. This table also includes summary information on the residue distributions that were prepared from the OPCRA food residue database as input for each food form. The actual DEEM-FCID™ input files and necessary rdf files will be made available upon request via CD-ROM or the internet for any interested party.

Residues in other foods were estimated using translated PDP data according to HED SOP 99.3, (USEPA, 1999b) as summarized in Appendix II.C.4. Translations included only residues for chemicals registered on the food being simulated. These foods account for about 1% of the per capita consumption of children 1-2 years old.

Surveillance monitoring data from FDA include extensive analysis of eggs and fish and indicate that OP residues would not be expected to

[13] Each food is assigned a percent of relative consumption, which was estimated in the following manner: 1) the per capita average consumption of each food was summed for all children in the survey for each of the two age groups; and 2) these consumptions were totaled for all foods in the survey and the individual sums for each food were expressed as a percent of the total. This measure of relative consumption is used as a general indicator of the potential significance of a given food in the diet of children. According to this measure of relative consumption, the PDP data (either directly or via OPP's standard policies for surrogating commodities) account for greater than about 90-95% of the per capita consumption by children 1-2 years old and children 3-5 years old.

occur in significant amount on these two categories of foods. These foods being supported by FDA data, i.e., eggs and fish, account for about 2% of the per capita consumption of children 1-2 years old.

PDP has analyzed high fructose corn syrup and found no OP residues but has not analyzed any other sugar or syrup sources. The FDA TDS has analyzed refined sugar and maple sugar and found no OP residues in 44 market baskets surveys (see http://www.cfsan.fda.gov/~comm/tds-mbs.html). A knowledge of the highly refined nature of sugars and syrups supported by the limited residue data mentioned above is the basis for the assumption that negligible residues of OP pesticides occur in sugars and syrups. Therefore, residues were assumed to be zero for these foods derived from sugarcane, sugar beet, and maple (this same assumption and assignment was made in the 2002 revised OP assessment). These foods, in total, account for about 2% of the per capita consumption of children 1-2 years old.

The food forms not included in the current assessment account for slightly more than 2% of the per capita consumption of children 1-2 years of age. No one single food form excluded from the assessment accounts for a significant portion of the consumption. Additional details can be found in Appendix II.C.1.

a. OP CRA Food Residue Database

The data manipulations necessary to prepare the PDP residue data for input into the risk equation are in principle very simple; actually performing these calculations for multiple chemicals and food commodities, however, can be cumbersome, tedious, and complicated. The residue data used in the 2002 Revised OP CRA consisted of approximately 1.5 million records of analytical data and sample information. With the additional 2002-2004 PDP data, the number of records increased to about 2.1 million. Processing factors account for several thousand additional records of information. For this reason, all the data manipulations in the original OP CRA and in this supplement/update were conducted using relational database techniques. As described in detail in the 2002 Revised CRA for the OP pesticides, the food residue database currently being used for this purpose consists of, among other things, four major data tables:

1. The Residue data tables contain about 2.1 million records, or essentially all of PDP sample and analyses data for OP pesticides.

2. The Processing factor data table contains all relevant processing factors for specific food form/chemical combinations. In this 2006 update, additional processing factors were included for the additional PDP commodities. Appendix II.C.5 provides a summary of the processing factors currently being used.[14]

3. The RPF Table which contains the Relative Potency Factors and FQPA Safety Factors for all chemicals included in the OP CRA Update.

4. The Translation Table provides bridging links between PDP commodity codes, such as *AJ* (apple juice), and all corresponding DEEM-FCID™ food forms, such as *Apple, juice cooked:canned;cook meth N/S*. This table also provides for the assignments of translated data between PDP commodities (such as between cantaloupe and watermelon). Appendix II.C.6 summarizes the links used in the OP CRA Update 2006. Bridging and translation of residue data from PDP source to CSFII food forms have been updated in this assessment and several adjustments and corrections were made in these assignments including new entries for food commodities not previously sampled by PDP, such as asparagus, cauliflower, and mushroom. All of the translations for the current (updated) assessment are presented in Appendix II.C.6.

These four tables are linked through common fields, including pesticide codes and commodity codes. Calculation queries are coded into the database so that all the pertinent residue records can be extracted and converted to index equivalent residues so that the results can be sorted and stored in various formats for further analysis. A cumulative residue calculation query which utilizes various parameters needed from the four tables described above is performed

[14] It should be noted that the absence of a processing factor in Appendix II.C.5 or a factor of zero indicates that the specific food form/chemical pair does not contribute to any residue distribution estimates. In some cases the absence of a factor is simply due to the fact that there are no detectable residues of that chemical in the database but in other cases it is due to the fact that a specific use is being excluded from the assessment because it is not being supported. Several commodities are not entered in the table at all because the residue analyses conducted on these foods were uniformly below detectable levels. Therefore, one should not use this table as a means of determining the uses included in the assessment. The appropriate starting point for this determination is Appendix II.C.7, which lists every food form included in the assessment. A factor of zero in the processing factor table in some cases is due to a correction of a former entry to account for actions taken as a result of mitigation/cancellation. Tolerances that were revoked due to risk management decisions resulting from single chemical aggregate assessments have been excluded (i.e. the processing factors set equal to zero) from the OP CRA Update.

on all of the food samples that are of interest. The results are then compiled in text files containing the cumulative distributions for each

b. Food Consumption Data

For this 2006 Update, food consumption data from USDA CSFII, 1994-1996/1998 was used. This is the same database that was used in the revised (as well as the earlier preliminary) OP CRA. This consumption survey is included as an integral ("hard-wired") component of the DEEM-FCID™ software. The 1994-1996/1998 CSFII contains survey data on 20,607 participants interviewed over two non-consecutive days. It incorporates the supplemental children's survey conducted in 1998 in which an additional 5,559 children, birth through 9 years old, were added. DEEM-FCID™ uses publicly available USDA/EPA recipes for conversion of foods (e.g, lasagna) reported on an "as eaten" basis in the survey to the recipes' component commodities (e.g., tomatoes, wheat, beef, milk, etc.) for which residue data are available.

Separate assessments were conducted on the various segments of the population as represented in the CSFII 1994-1996/1998. As was done in the 2002 OP CRA, the current updated assessment includes the following standard age groups:

- Infants less than 1 year old
- Children 1-2 years old
- Children 3-5 years old
- Children 6-12 years old
- Youths 13-19 years old
- Adults 20-49 years old
- Adults 50+ years old
- Females 13-49 years old

The most highly exposed population groups in this cumulative assessment are children 1-2 and children 3-5 years old; subsequent analyses of the results reported in this document will emphasize results for these age groups.

5. Hazard Data Used in the Food Risk Assessment

Section I.B of this 2006 Update describes the hazard portion of this risk assessment in detail. Briefly, methamidophos was chosen as the index chemical, and relative potencies of the OP chemicals were based on female rat brain cholinesterase inhibition. The point of departure (BMD_{10}) was 0.08 mg/kg body weight/day. Assignments of FQPA Safety Factors for this OP cumulative assessment were made for each individual chemical in the assessment by applying these factors directly to the residues. For example if a chemical's FQPA factor is determined to be 10, then all residues of that chemical would be made ten times as toxic. Since the FQPA factors were incorporated at the individual chemical level, the target MOE for the assessment is 100 (10 for inter-species and 10 for intra-species).

An FQPA factor of 10 was applied by default to each chemical in the assessment unless toxicological evidence provided reliable data showing that the FQPA factor should be modified. Based on additional toxicological studies, the FQPA factors for acephate, azinphos-methyl, chlorpyrifos, DDVP, dicrotophos, dimethoate/omethoate, disulfoton, fosthizate, methamidophos, and terbufos were reduced. Further information and rationale are provided in Section I.B of this document.

6. Results

a. Presentation of Margins of Exposure (MOE)

The cumulative food exposure assessment for OP pesticides on food commodities was conducted for eight age groups: infants of less than one year, children 1-2 years old, children 3-5 years old, children 6-12 years old, youths 13-19 years old, adults 20-49 years old, adults 50+years old, and females 13-49 years old. Table I.C-1 provides the single day exposure (in mg/kg) and margin of exposure (MOE) values at various percentiles for the eight age groups.

Table I.C-1 Exposure and MOE Values for the Single-Day OP Cumulative Food Assessment.

	95th Percentile		99th Percentile		99.9th Percentile	
	Exposure (mg/kg)	MOE[a]	Exposure (mg/kg)	MOE[a]	Exposure (mg/kg)	MOE[a]
All infants	0.000049	1600	0.00028	290	0.0013	60
Children 1-2 yrs	0.00018	440	0.00064	130	0.0026	30
Children 3-5 yrs	0.00016	510	0.00051	160	0.0023	34
Children 6-12 yrs	0.00011	750	0.00034	230	0.0014	55
Youths 13-19 yrs	0.000070	1100	0.00023	350	0.00088	90
Adults 20-49 yrs	0.000081	990	0.00028	290	0.0011	75
Adults 50+ yrs	0.000092	870	0.00034	240	0.0012	64
Females 13-49 yrs	0.000077	1000	0.00027	300	0.0011	75

[a] As explained in Sections I.B and I.G of this document, the exposures shown here reflect single day (acute) exposures at the indicated percentile, but the MOEs are based on the POD from repeated exposure over a period of 21 days Therefore, this is expected to overestimate of risk. See Appendix Xx.xx for additional details.

In addition to the single day dietary exposure assessments, a 21-day rolling average assessment was conducted for all of the age groups (Table I.C-2). Additional technical details and information on these modes of analysis were presented in the 2002 Revised OP CRA. Based on toxicological consideration pertaining to the dietary point of departure, 21-day average exposure values should be evaluated in addition to the single day dietary exposure values (see Sections I.B and I.G for more details).

Table I.C-2 Exposure and MOE Values for the 21-Day OP Cumulative Food Assessment.

	95th Percentile		99th Percentile		99.9th Percentile	
	Exposure (mg/kg)	MOE	Exposure (mg/kg)	MOE	Exposure (mg/kg)	MOE
All infants	0.000097	820	0.00017	480	0.00048	170
Children 1-2 yrs	0.00015	550	0.00032	250	0.00076	110
Children 3-5 yrs	0.00012	670	0.00027	300	0.00081	99
Children 6-12 yrs	0.000099	810	0.00018	460	0.00049	170
Youth 13-19 yrs	0.000097	820	0.00011	740	0.00027	300
Adults 20-49 yrs	0.000098	820	0.00013	610	0.00028	280
Adults 50+ yrs	0.000099	810	0.00016	510	0.00033	240
Females 13-49 yrs	0.000098	820	0.00013	620	0.00028	290

Appendix II.C.7 contains a complete listing of the food forms in the DEEM-FCID™ software that were included in this assessment. This table also includes summary information on the residue distributions that were prepared from the OPCRA food residue database as input for each food form. The actual DEEM™ input file and necessary rdf files will be made available upon request.

b. Analysis of Commodity-Chemical Combinations that Significantly Contribute to the Upper Percentiles of the Exposure Distribution

The "Commodity Contribution Analysis" feature of DEEM-FCID™ software is able to identify the specific foods and food forms that contribute to the upper percentiles of an exposure distribution. This capability was used in this updated food assessment and, in combination with the chemical/commodity specific information maintained in the food residue database described above, used to assess both foods and pesticides which predominate at the high end of the exposure distribution. The data summarized here were obtained by examining the exposure distribution interval from the 99.8th percentile to the 100th percentile. Table I.C-3 lists – in rank order -- the top 20 of the food forms appearing at or above the 99.8th percentile from a Monte Carlo assessment of the exposure of children 3-5 years old.

Table I.C-3 Partial Summary of Foods and Food Forms Occurring in the Top 0.2 Percentile of Exposure for Children 3-5 in OP CRA.

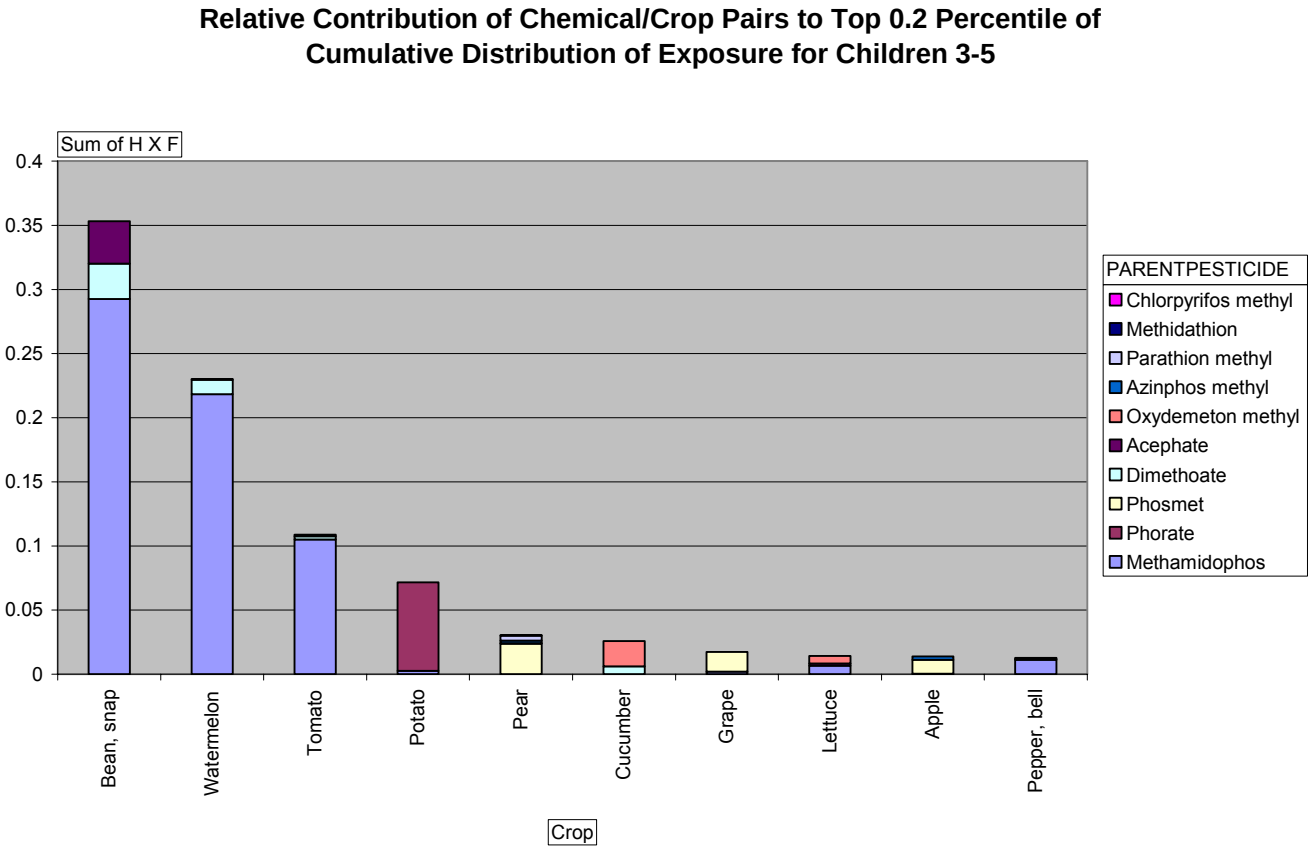
Food	Food Form	N	Fraction of Total Exposure
Bean, snap, succulent	Cooked; Fresh or N/S; Boiled	2952	0.31
Watermelon	Uncooked; Fresh or N/S; Cook Meth N/S	1422	0.23
Tomato	Uncooked; Fresh or N/S; Cook Meth N/S	979	0.07
Potato, tuber, w/o peel	Cooked; Fresh or N/S; Boiled	435	0.04
Grape	Uncooked; Fresh or N/S; Cook Meth N/S	168	0.03
Pear	Uncooked; Fresh or N/S; Cook Meth N/S	406	0.03
Tomato	Cooked; Fresh or N/S; Boiled/baked	327	0.02
Bean, snap, succulent	Uncooked; Fresh or N/S; Cook Meth N/S	118	0.02
Cucumber	Uncooked; Fresh or N/S; Cook Meth N/S	144	0.02
Potato, tuber, w/o peel	Cooked; Frozen; Fried	245	0.02
Apple, fruit with peel	Uncooked; Fresh or N/S; Cook Meth N/S	333	0.01
Lettuce, head	Uncooked; Fresh or N/S; Cook Meth N/S	161	0.01
Cucumber	Cooked; Canned; Cook Meth N/S	109	0.01
Pepper, bell	Uncooked; Fresh or N/S; Cook Meth N/S	215	0.01
Plum	Uncooked; Fresh or N/S; Cook Meth N/S	196	0.01
Strawberry	Uncooked; Frozen; Cook Meth N/S	67	0.01
Bean, snap, succulent	Cooked; Canned; Boiled	241	0.01
Tomato	Cooked; Fresh or N/S; Baked	207	0.01
Peach	Uncooked; Fresh or N/S; Cook Meth N/S	185	0.01
Honeydew melon	Uncooked; Fresh or N/S; Cook Meth N/S	72	0.01

Summing across the different food forms, OP residues on snap beans account for approximately 35% of the total exposure in the tail of the distribution (i.e. the 99.8th to the 100th percentile) followed by watermelon and tomato which account for roughly 23% and 11% respectively.

To identify the associated pesticides, all of the food forms in the above table were linked with the corresponding residue distributions that had been generated for the cumulative assessment. The individual chemical contributors to these distributions were extracted from the OP CRA food residue database used to generate the distributions. Thus, the relative percent contributions of food forms derived from DEEM-FCID™ were combined with the relative percent contributions of chemicals to each food form's residue distribution to estimate the relative contribution of each chemical to the interval being examined. These data were further collapsed and summarized by combining all food forms to the crop level, for example, fresh grapes, raisins, and grape juice were all combined under the crop name "Grapes", and so on. All metabolites, degradates, and isomers were

combined for each active ingredient included in the assessment. Figure I.C 1 is a graph which illustrates the relative contribution of each chemical/crop combination to the exposure in upper end of the distribution of exposure values based on combining the information about food forms and residue distributions. The linkage of the DEEM-FCID™ output and the OP CRA food residue database information on chemical/crop specific contributions are summarized in Appendix II.C.8.

Figure I.C-1 OP Chemical/Crop Pairs that Significantly Contribute to Upper Percentile of Exposures.



7. Discussion

A number of choices and assumptions made in the conduct of the 2006 Update may differ from previous single-chemical assessments. The

following discussion is intended to provide some background on the impact of choices that are unique to this assessment.

a. Some PDP Residue Data Were Excluded

The assessment includes only chemical/crop combinations currently being supported for registration in the United States or with import tolerances or had violative residues in PDP. Therefore, residues representing cancelled and phased-out uses are excluded. That is, residues in the OP CRA food residue database that do not represent supported section 3 registrations, special local need (SLN) uses, or supported import tolerances are excluded from the assessment. The criteria listed in this paragraph are intended to ensure that the cumulative assessment simulates the residue pattern that will result from ongoing mitigation actions in the re-registration of OP pesticides.

b. Composite Samples Were Used to Estimate Residues in Single-Servings as Consumed

Only the residue data from composite samples were utilized in this assessment. Composite samples generally contain approximately five pounds of a commodity. A single composite sample may therefore contain several individual servings of some foods. For purposes of the present assessment, it is assumed that residues reported in composite homogenates adequately reflect the residues in any given single-serving contained in that homogenate. In other words, the level of residues in a five pound composite sample of potatoes would be similar to the level of residues in any one potato in the composite sample. Therefore, no attempt was made to "decomposite" residue values to simulate residues that might be present in the single-servings contained in the PDP composite sample. PDP has conducted single-unit sampling for apples, pears, and peaches since 1998. A comparison of the residue levels in these single-servings to the residues on comparable composite samples indicate that use of composite samples will not result in a significant under- or overestimation of exposure at the upper percentiles of the distribution.

c. PDP Samples Were Assumed to Reflect Residues in Foods Prepared for Consumption

The PDP program generally collects foods at wholesale distribution centers and warehouses and stores them frozen until analysis. Foods are washed and inedible portions are removed before analysis but these foods are not further cooked or processed. Processing factors (see Appendix II.C.5) were applied to the residue data in this

assessment. These factors were taken from the most recent single-chemical dietary exposure assessments for the OPs. Generally when no information is available, the processing factor is set equal to one indicating that processing would not reduce the residue. Therefore, some storage or process-related dissipation of residues may occur but is not accounted for. Even though the processing factors may result in some overestimation of residues in processed foods, the impact on this assessment is expected to be minimal since many of the food forms that are present in the upper ends of the exposure distribution are either uncooked (raw) food forms in and of themselves or are supported by PDP residue data that implicitly incorporate processing factors (e.g. canned green beans).

d. Residue Data Were Assumed to Reflect Co-occurrence of OPs in Single-Day Diets

One reason for conducting the assessment of PDP residue data on a sample-by-sample basis is to maintain the connections in multi-analyte occurrences on these samples. In other words, it is assumed that the PDP sampling and analysis protocols capture the co-occurrence of OP pesticides. Appendix II.C.9 demonstrates the extent of this measured co-occurrence in the PDP program between 1994 and 2004. It can be seen in this table that a majority of PDP samples were reported as containing no detectable residues at all. For those that contained detectable residues, single residues were most prevalent but many multi-residue samples were found.

e. All OPs of Concern on an Analyzed Food Sample Were Assumed to be Accounted for in the Residue Analysis

All residue analyses are subject to the limitations of the sensitivity of the analytical methods. Many of the samples analyzed are reported as being below the analytical method reliable limit of detection (LOD). It has been the usual practice in Agency assessments on individual pesticides to assume that residues in non-detectable samples are present at ½ LOD of the analytical method in samples that were harvested from treated fields. Thus, for purposes of estimating residues in samples reported as <LOD, a proportion of the samples equal to the estimated percent crop treated is assigned a residue level of ½ LOD and the remaining samples, which are assumed to come from untreated crops, are assigned a residue value of zero. This procedure becomes problematic for a cumulative assessment. It is not enough to estimate the percent crop treated for each of the pesticides in the cumulative assessment: it is also important to consider the potential for co-occurrence of multiple residues on the same crop.

In the current assessment, it is assumed that all OP residues reported as non-detectable are absent from the sample, i.e., they are assigned a value of zero. In a complex analysis such as this cumulative analysis in which there are abundant samples with detectable residues, the use of a value of "zero" for non-detects would not be expected to greatly impact the outcome of the exposure assessment at the highest percentiles. This was tested in an earlier stage of the assessment and reported in the case study that was presented to the SAP in December of 2000. Cumulative food exposure assessments were conducted using two extreme default assumptions: 1) all non-detects = 0, and 2) all non-detects = ½ LOD for the chemical with the greatest number of detectable residue findings on a given food commodity. It is reasonable to assume that the chemical most often detected on a given food would also have the greatest number of residues below the limit of detection on that food. Under the conditions of the case study, the two extremes showed essentially no significant difference in exposure above the 95th percentile of exposure. At the lower percentiles of exposure, the difference in using zero versus ½ LOD for non-detectable residues on cumulative exposure was much greater; however, the overall exposure levels were so low they would not be considered to be of concern.

f. PDP Residue Data Were Translated in some Cases to Foods for which No Residue Data Were Available

In chemical-specific dietary exposure assessments, the Agency routinely translates residue data from one food commodity to related ones if the pesticide use patterns are similar on these commodities (USEPA, 1999b). For example, data on cantaloupes are often used as surrogate data for watermelons and other melons. In the current assessment, translations of the residue data were made using the translation scheme presented in HED SOP 99.3 (USEPA, 1999b) in order to ensure representation of the maximum number of commodities possible. The allowable translations are summarized in Appendix II.C.4. In making these translations, the only residues included were those that could occur on the simulated food from current registrations of OP pesticides. The uncertainty in this scheme is not expected to have a major impact on the assessment because the foods being translated comprise a relatively small portion of the per capita consumption by children (See Appendix II.C.1 for confirmation of this fact). An analysis of foods in the higher percentiles of exposure in this assessment has confirmed that translated foods do not significantly impact that portion of the distribution.

g. The Food Exposure Portion of this Cumulative Assessment is Considered to be Constant throughout the Year and Across Regions

It is currently assumed that the food distribution and storage systems in the United States result in essentially a national distribution of the major foods in our diet that is constant throughout the year. For some of the seasonal changes in availability of certain foods, PDP has designed its sampling program to concentrate on these time frames so that the residue data should reflect the foods as available to the consumer. This applies to imported commodities also. For the water portion of dietary exposure, it is recognized that the potential for residues is not constant nationwide and like food, it is also not constant throughout the year (i.e., higher runoff in the spring means higher levels in surface water at that time). The national food estimate is combined with regional water assessments to provide a series of regional dietary assessments.

8. Conclusions

The food component of the OP CRA 2006 Update is considered to be highly refined and to provide reasonable estimates of the distribution of exposures across the United States. The exposure estimates for food are based on residue monitoring data from the USDA's PDP program supplemented (qualitatively) with information from the FDA Surveillance Monitoring Programs and its TDS. The PDP data provide a very reliable estimate of pesticide residues in the major children's foods and account, directly or indirectly through commodity the use of commodity surrogates, for more than 90-95% of consumption for children. The reliability of the food component of this assessment is also supported by its use of the food consumption data from the USDA's CSFII 1994-1996/1998. The CSFII surveyed more than 20,000 individuals over two non-consecutive days. The survey provides a detailed representation of the food consumption patterns of the US public across all age groups, during all times of the year, and across all 50 states. Thus, EPA has confidence that the distribution of risk estimates for food is well-predicted and reasonably reflects risks to the US population.

D. Residential OP Cumulative Risk

As more fully described in Section I.A of the document, this section on residential exposure serves to update and supplement the Revised OP Risk Assessment document released in 2002. As such, the reader is referred to the 2002 document which contains more detailed specifics on approaches, calculations, and methods used to evaluate the residential aspects of cumulative exposure.

Since the release of the 2002 document, OPP has mitigated a number of uses with respect to several OPs. As described in more detail in Chapter 1 of this supplement, DDVP uses associated with foggers, lawn products, large pest strips, and crack and crevice sprays have been requested to be cancelled or modified in a way to reduce risks below the Agency's level of concern. Additionally, all uses of fenthion and fenamiphos have been cancelled. These changes are summarized in Table I.D-1 below.

Table I.D-1 Changes in OP Use Patterns Since the 2002 Revised OP CRA

OP Pesticide	Product	Change in Use Pattern
DDVP	21 g pest strip, total release fogger, lawn products, 100 g pest strip, and crack and crevice	Uses requested to be cancelled
DDVP	65 and 80 pest strip	Use change: only for use in specified unoccupied areas and dwellings that remain unoccupied for more than 4 months
Fenthion	Public health use	Use cancelled
Fenamiphos	Golf course use	Use cancelled
DDVP	16 g pest strip	Use added

The remaining use scenarios are identical to those in the 2002 document and -- apart from brief mention here in the chapter -- the reader is referred to this earlier document for more complete details with respect to input data and modeling assumptions.

1. Introduction

As was done in the 2002 document, OPP employed a calendar based model (Calendex™) to address the temporal aspects of the residential use of pesticides. A calendar-based approach provides the ability to estimate daily exposures from multiple sources over time to an individual and is in keeping with two key tenets of aggregate risk assessment: 1) that exposures -- when aggregated -- are internally consistent and realistic; and 2) that appropriate temporal and geographic linkages or correlations/associations between exposure scenarios are maintained. The Calendex™ software allows OPP to delineate the critical timing

aspects of seasonal uses of OP insecticides that result in exposure to pesticides during the year. Calendex also enables OPP to identify potential risks caused by co-occurrence of exposures from multiple routes and pathways (e.g., near simultaneous same-day exposures through drinking water and residential uses). This includes the exposure from home lawn and garden treatments, pesticides used on golf courses, and applications made by governmental entities for the control of public health pests such as wide area mosquito sprays.

In nearly all cases, the residential exposure scenarios in this 2006 OP CRA Update were developed using proprietary residue and exposure data. Exposure factors such as breathing rates and durations of time spent indoors or outdoors were taken from various references including US EPA/ORD/NERL Consolidated Human Activity Database (CHAD), and the Agency's Exposure Factors Handbook (USEPA, 1997a). In this assessment (as in the 2002 Revised assessment), the full range of exposure values – expressed as uniform, log-normal or cumulative distributions -- are used, where appropriate, rather than relying solely on measures of central tendency. While the dietary and drinking water assessment address a portion of the oral exposure route, the residential assessment considers the dermal and inhalation exposure routes as well as the oral route based on the mouthing behavior of young children.

EPA registered labels were also used extensively in developing and defining appropriate use scenarios. However, these labels -- while useful for establishing site/pest relationships and recommendations for applications -- generally cannot inform the temporal aspects of regional pesticide use. Thus, OPP has relied on other sources of pesticide use information, including the National Home and Garden Pesticide Use Survey (NHGPUS) data and information available in State Cooperative Extension Service publications. These data resources were comprehensively used to identify information such as frequency of applications, the type of application equipment used, and the type of clothing worn while making those applications. State Cooperative Extension Service recommendations were used to establish regional windows of pesticide applications based on the observed appearance of insects such as white grubs on lawns in a particular locality.

2. Scope of Regional Assessments

Several of the OP pesticides are registered for residential type uses. These include bensulide and trichlorfon on golf courses and/or residential lawns; acephate, disulfoton, and malathion for home gardens; malathion, and naled for public health uses; DDVP for indoor use as a pest strip and aerosol spray; and tetrachlorvinphos and DDVP for pet uses.

In the 2002 revised OP assessment, the U.S. was divided into seven regions (Florida, Northwest, Arid/Semi-arid West, Northeast/North Central, Humid Southeast, Lower Midwest, and Mid South) designed to capture various residential use patterns and drinking water vulnerabilities. For the 2006 OP CRA Update, OPP performed one regional analysis that included all OP residential uses. The residential exposure scenarios for Region A (Florida) are considered to be reflective of the worst-case conditions associated with this portion of the U.S since there is little or no period of insect dormancy in the Southern portion of the U.S, the growing season is longer than the rest of the U.S., and the pest pressures are greater. Therefore, for the OP residential assessment, OPP created a region that comprised all Region A residential uses plus all other OP residential uses that were previously excluded from Region A. This region is referred to as "Region X" and provides a worst case combination of all OP residential uses**.** Additionally, for each residential scenario in Region X, worst-case assumptions regarding percent of households treated and application frequency were used. For example, if Region G included a garden scenario that assumed a greater number of seasonal applications, or a greater number of households treated than those listed for the same scenario in Region A, these inputs (i.e, higher percentage of households being treated and higher number of applications) would have been used to assess the garden scenario in Region X. Thus, this update provides a highly conservative assessment of risk through residential exposures.[15]

3. Residential Scenarios

The Residential Scenarios addressed in this document represent critical OP uses that have the potential for significant exposure or risk when considered in a cumulative assessment. These are:

- Golf course and lawn care applications,
- Home gardens,
- Wide area Public Health sprays,
- Indoor Uses (includes impregnated pest strips (limited to closets and cupboards) and aerosol spray can),
- Pet Treatments (includes pet, collar, aerosol, liquid, and powder uses)

[15] Since Region X is a composite of worst case conditions, there may be a tendency to overestimate risk. However, OPP believes this bias will not affect the results, particularly since all OP residential uses other than DDVP are secondary contributors to overall residential exposure.

Due to changes in the use pattern for DDVP, the residential assessment for the this update to the revised OP CRA focuses only on updating the DDVP exposure scenarios; the inputs and calculations for the remaining use scenarios remain the same and are identical to those described in the 2002 Revised OP assessment (except, of course, for those scenarios in which uses were cancelled in which case they are entirely removed from the assessment[16]).

a. Golf Course and Lawn Treatments

The golf and lawn scenarios assessed in this update are identical to those assessed in the 2002 revised OP CRA. Specifically: acephate, bensulide, and trichlorfon are considered for golf course uses on fairways, greens, and tees. Of these three pesticides, bensulide and trichlorfon are also registered for home and lawn uses by home owners or lawn care operators (LCOs) and are also incorporated into this update. Specific details regarding these uses and inputs to these scenarios are listed in the Residential Chapter (I.D.3) of the 2002 revised OP CRA.

b. Home Gardens

The home garden scenarios assessed in the update are identical to those assessed in the previous OP CRA and consider ornamental and edible food garden scenarios. Specifically, ornamental uses of acephate, disulfoton, and malathion and food garden uses of malathion were considered in this report. Details of these uses are listed in the previous revised OP CRA Residential Chapter (I.D.3.b).

c. Public Health Uses

The public health scenarios assessed in this update are identical to those assessed in the 2002 revised OP CRA, and include malathion, and naled. Details of these uses are listed in the previous revised OP CRA Residential Chapter (I.D.3.c).

d. Indoor Uses

DDVP is the sole OP pesticide with indoor registrations. Recent mitigation for DDVP has resulted in the request for voluntary cancellation of several uses. Specifically, the total release fogger, crack and crevice, the 100 g pest strip, and lawn products have been requested to be cancelled and therefore are not included in this

[16] The DDVP total release fogger, crack and crevice, the 100 g pest strip, and lawn products have been requested to be cancelled and therefore are not included in this assessment. Fenthion public health use and fenamiphos golf course uses were also cancelled.

assessment. The indoor uses that remain for DDVP-- and for which this updated assessment has estimated exposures -- are the 5 gram (0.95 g of ai) pest strip, the 10 gram (1.9 g of ai) pest strip, the pet collar (containing 2.2 grams ai), and the indoor aerosol spray. While two of the large strip (65g and 80g) uses will remain, the labels will be modified to include language indicating use only in specified unoccupied areas and dwellings (such as vacation homes, cabins, etc) that remain unoccupied for more than 4 months. Therefore, since restricted use of the large strips is not expected to result in significant exposure, the indoor use of large DDVP pest strips was not assessed in the report.

The DDVP registrant also will request registration of a new 16 gram pest strip. For this reason, this update includes consideration of the 16 gram pest strip use. The 16 gram pest strip will have label language similar to the small DDVP pest strips. Specifically, the 5 gram, the 10 gram, and 16 gram pest strips will be labeled for use in closets, wardrobes and cupboards within residential dwellings. These pest strips may also be used in storage areas, such as garages, crawl spaces and attics.

Due to the physical-chemical properties of DDVP, only the inhalation pathway was assessed. Exposure via the oral non-dietary and dermal routes are considered minimal relative to inhalation exposure.

Pest Strips:

The DDVP small pest strips (5g, 10 g and 16 g) scenarios represented here are similar to the pest strip scenarios assessed in the previous OP CRA (see pages 23 and 24 of the Residential Chapter of the Revised OP CRA (I.D.3.d) for detailed explanation of post-application inhalation exposure calculations). In short, only post-application inhalation exposure was estimated for adults and children, with applicator exposure considered to be negligible. Air concentrations in this updated OP CRA were estimated from the measured concentrations from a study using the 80 gram pest strip (Collin and DeVries, 1973). Since the use of a smaller pest strips were assumed to produce a proportionately smaller air concentrations, reduction factors were calculated to predict air concentrations for smaller sized strips based on the ratio of the amount DDVP in the larger strip to that in the smaller strips. Air concentrations were then multiplied by the calculated reduction factor for each small pest strip scenario (5g, 10g, and 16 g). Estimated indoor inhalation exposure resulting from the use of DDVP pest strips also incorporated the same

CHADs data and MET_TIME calculations as were used in the 2002 revised OP CRA (and are described fully there).

Assumptions regarding typical use and usage of DDVP pest strips were not altered from the previous cumulative assessment (See pages 26 and 27 of the previous assessment for details): use information for number of households using DDVP pest strips indoors was taken from the NHGPUS (1991), and the use of pest strips was assumed to occur year round with strips replaced once every 16 weeks. Based in part on the information provided in NHGPUS, 2 percent of the homes were assumed to use DDVP pest strips.

Aerosol Spray:

Applicator exposure was assessed for homeowners using a pressurized spray can of DDVP in their homes. This scenario was not assessed in the 2002 Revised OP CRAt document and is new to this update. Applicator inhalation exposure was calculated by multiplying the inhalation unit exposure value (in mg/ounce applied) by the amount used (ounces/day). The unit exposure data used to assess inhalation exposure for homeowner applicators of the pressurized aerosol was derived from data in the Pesticide Handlers Exposure Database (PHED) v 1.1 (Knarr, 1988). A distributional analysis of this data determined that it was described by lognormal distribution (mean = 0.34 mg/oz ai and standard deviation =0.27 mg/oz ai; see Appendix II.D for details of distributional analysis). Homeowners were assumed to apply approximately 2 ounces of spray during any single treatment (based on information from the Residential Exposure Joint Venture (REJV) survey). Other use pattern information for the aerosol spray can scenario (such as percent household use, frequency of application and season of use) are based on use information from NHGPUS for indoor products.

Data are not available to model post-application inhalation exposure resulting from the used of the DDVP pressurized can scenario. Therefore, post-application inhalation exposure was not assessed for this use. However, due to the number of other DDVP indoor uses considered in this assessment, post-application exposure resulting from the use of DDVP indoor aerosol products is expected to be a minor contributor to overall post-application inhalation exposure.

e. Pet Uses

Two OP pesticides remain for use on pets: tetrachlorvinphos (TCVP) (aerosol, pump, flex collar, and powder) and DDVP (flea collar only).

Tetrachlorvinphos was evaluated in this assessment as an aerosol, pump, or powder flea and tick treatment for pets. While tetrachlorvinphos is also available in impregnated form in pet collars, this updated assessment considered only tetrachlorvinphos pet treatment using the aerosol, pump, or powder form (and not the impregnated collar form), as these uses are believed to result in equal or higher exposures than the pet collar use. This is based on the (reasonable) assumption that shampooing a dog will result in greater exposure than merely securing a collar around a dog's neck. Exposure assessments were performed for both applicators and non-applicators (i.e., post-application exposures). For applicators, both dermal and inhalation routes were considered. For post-application exposures, only the dermal and oral (hand-to-mouth) routes were considered. All exposure inputs for the tetrachlorvinphos pet scenarios are identical to those used in the 2002 Revised OP CRA (see section I.D.3.e of the previous OPCRA Residential Chapter for details)

In this updated OP CRA, exposures resulting from the use of DDVP pet collars are also assessed. This assessment considered only post-application inhalation exposure resulting from the use of DDVP pet collars. Exposure via the oral non-dietary and dermal routes are considered minimal relative to inhalation exposure and therefore were not included in this assessment. The DDVP pet collar assessment is similar to the pest strips assessments. In effect, pet collars were treated as "mobile" pest strips. Air concentration data was based on the same study as was used to model potential pest strip exposure (Collin and DeVries, 1973). Again, the grams ai in the large strip (14.88 g ai) was divided by the grams ai in the pet collar and a reduction factor was calculated. The use information regarding number of households using DDVP pet collars was inferred for chemical-specific pet collar use information from NHGPUS. The assessment also assumed that pet collars are used year-round.

4. Other Considerations: Oxons

The Agency has evidence to indicate that a number of OP pesticides may be transformed in the environment to oxons. Limited data also suggested that oxons may be more toxic than the parent OP. Some residential-use OP pesticides are themselves oxons (such as acephate, naled, DDVP, and TCVP) or convert to oxons (e.g., trichlorfon to DDVP). These OP pesticides were considered in the residential assessment using chemical-specific (i.e., oxon) residue data. Additionally, some other OP pesticides degrade to form oxons that themselves are not registered active ingredients. Specifically, these include disulfoton, bensulide, and malathion. This residential

assessment considered oxon exposure resulting from residential uses of disulfoton in ornamental garden treatments, bensulide lawn and golf course applications and malathion public health uses. Since there are no available residue dissipation or decay data to quantitate the amount of oxon formation resulting from residential uses of bensulide, disulfoton, or malathion, a sensitivity analysis was conducted to determine the relative oxon contribution to overall cumulative risk. OPP performed this sensitivity analysis by increasing bensulide and disulfoton residues by a factor of 10 and malathion residues by a chemical-specific potency factor of 61. These factors further assume 100% oxon conversion for bensulide/disulfoton and 10% oxon conversion for malathion[17]. An exposure analysis (combining exposure resulting from oxon formation with other residential uses, food contribution, and worse case water) was then modeled to generate 21-day rolling average MOEs over the course of one calendar year. 21-day analyses done with and without oxon contribution did not significantly differ, proving the relative negligible contribution of oxons to overall cumulative risk.

5. Summary

This assessment relied upon the best available data from all sources that could be identified. Sources included chemical specific and task force- generated data, as well as data from the scientific literature. Graphs for the Calendex 21 day analysis for children 1 to 2 years old, at the 99.9 percentile are presented below (and are discussed more fully in the cumulative chapter of this document). Graphs are also available for all other subpopulations at the 95th, 99th, and 99.9 percentiles of exposure. These graphs are available in Appendices III.A through III.E of this document.

In summary, the residential assessment of the 2006 OP Update assumes a worst case combination of all OP residential uses and reflects worst case pesticide use information. All resulting MOEs (dermal, incidental oral, and inhalation) associated with all residential uses of the OP pesticides exceed 100 and therefore are not of concern (MOEs are consistently greater than 150). Figures I.D 1 and 2 show results for the 21 day analysis of children 1 to 2 years old. However, similar conclusions can

[17] Monitoring data for most substrates (e.g., turf and leafy foliage) indicate malaoxon formation of < 1% of the total malathion deposited from aerial application of malathion bait spray. However, some data sources show transformation to malaoxon as high as 10%. Thus, the OP CRA assumed 10% conversion to malaoxon resulting from the public health uses of malathion. This upper bound assumption regarding oxon formation was done to provide a conservative estimate of risk.

be drawn for all other populations (see Appendices III.A through III.E for further details).

The results for children 1-2 years old (see Figure I.D 1 below) indicate that incidental oral MOEs are not of concern. Additionally, dermal MOEs are well above the level of concern for most of the year. However, a portion of the summer months (days 186 through 243), MOEs go down to approximately 150. Further analysis has determined that these MOEs are the result of trichlorfon lawn exposure. This decrease in MOEs is attributed to the application pattern information for the trichlorfon lawn scenarios. Lawn applications of trichlorfon are expected to occur in the summer months to treat lawn pests, such as grubs, webworms, billbugs, mole crickets and chinch bugs. The inhalation MOEs are consistently the lowest and therefore present the greatest risk. By removing DDVP from the residential assessment, OPP determined that the inhalation MOEs result entirely from exposure from the DDVP indoor uses. This is illustrated in Figures I.D 1 (including all OP residential uses) and I.D 2 (including all OP residential uses except DDVP): when all DDVP use is removed from the assessment, no inhalation risks are apparent.

As seen in Figures I.D 2, the inhalation pathway is the major contributor to overall residential exposure. Residential inhalation exposure primarily results from indoor post-application exposure to DDVP pest strip and pet collars. Indoor exposure to DDVP pest strips and pet collars is continuous for the effective life of the product (up to 16 weeks). DDVP pest strips and pet collars are constantly emitting sources that dissipate over the duration of use. For this reason, the 21 day analysis more appropriately addresses DDVP exposure than the single day analysis. Further, since DDVP is a major contributor to the overall residential exposure, the 21 day analysis also is more suitable to assess overall residential exposure and risk. Results for the single day analysis, therefore, are not presented in this section.

Figure I.D-1 21-Day Analysis for ALL OP Residential Uses Including DDVP; MOEs at the 99.9th Percentile.

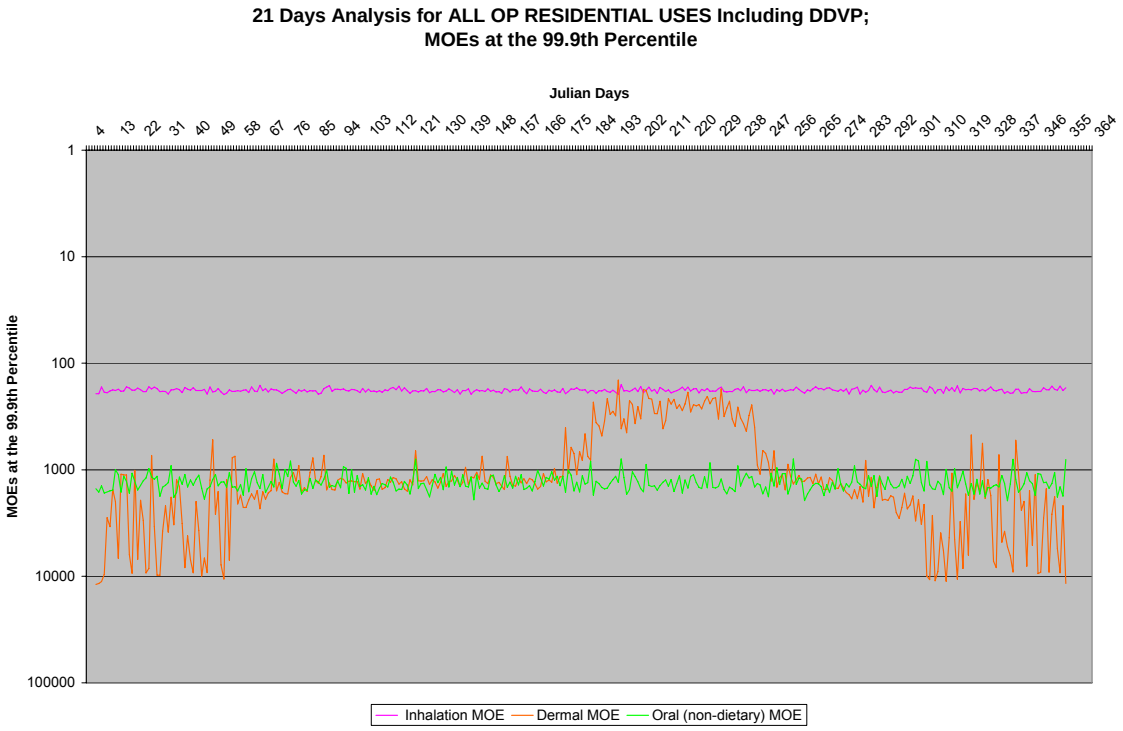
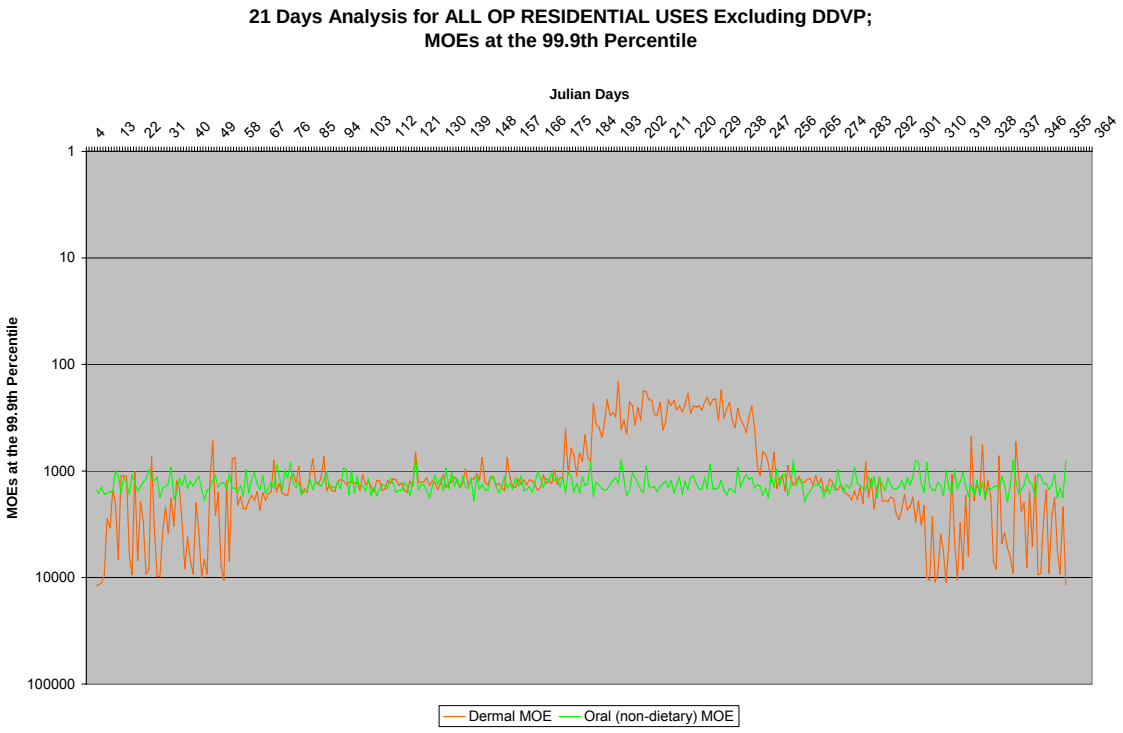


Figure I.D-2 21-Day Analysis for ALL OP Residential Uses Excluding DDVP; MOEs at the 99.9th.



E. OP Cumulative Exposure in Drinking Water

1. Introduction

Since the 2002 revised OP CRA was published, usage practices for a number of the OP pesticides have changed as a result of the Agency's risk management decisions. This section describes the changes that were made in the modeling inputs used for the drinking water exposure estimates and characterizes the resulting regional drinking water exposure distributions.

This drinking water exposure assessment includes an update on the characterization of the potential impacts of the conversion of some OP pesticides to oxon transformation products as a result of oxidation during standard drinking water treatment processes. This qualitative update is based on additional lab studies that assess the potential for oxon formation and on additional toxicity information.

EPA estimated distributions of individual and cumulative OP pesticide residues in drinking water in high potential exposure areas across different regions of the country. Based on this drinking water exposure assessment, cumulative OP exposures from drinking water are expected to be below levels of concern. Fate and transport properties of the OP pesticides, available monitoring data, and individual chemical assessments indicate that OP residues are not expected to occur at appreciable levels in ground water sources of drinking water. For surface water sources of drinking water, OP residues are expected to reach single- to sub-parts per billion (µg/l) during periods of high-volume runoff following application. These peak concentration periods are generally of short duration (days to weeks). Modeling estimates were also compared with available water monitoring data in the 2002 OP CRA; while estimated concentrations of some individual OP pesticides were less than reported detections, most were on the same order or greater than those found in monitoring studies. Subsequent risk management actions (cancellations, rate reductions, etc.) have resulted in lower cumulative OP concentrations in most regions.

A number of OP pesticides have the potential to convert to more toxic oxon transformation products as a result of chlorination/oxidation during standard drinking water treatment. Additional studies conducted since 2002 confirm the potential for OP pesticides to form stable oxon transformation products as a result of chlorination. Less data are available on the relative magnitude in which the oxons are more toxic than the parent. For those oxons with insufficient toxicity information, EPA bracketed the potential differences in toxicity between the parent and the oxon between 10X and 100X. Using protective assumptions (100%

conversion from the parent to the oxon, instantaneous transformation to oxon with no degradation), EPA estimated that the oxons would not appreciably change the cumulative OP distributions with a 10X oxon adjustment factor. However, with a 100X adjustment factor, estimated peak cumulative concentrations increased by as much as 35-50X in one region. Additional data regarding oxon toxicity for methidithion are needed.

2. Conceptual Model for Drinking Water Exposure

The 2002 revised OP CRA provides a detailed description of the conceptual model used for estimating the cumulative exposure from OP pesticides in drinking water, including the supporting information used to develop the model. The conceptual model for exposure from OP residues in drinking water in the 2006 update remains the same as in the 2002 assessment. The goal of the drinking water exposure assessment is to estimate distributions of concentrations of co-occurring OP pesticides in drinking water for various regions of the country, taking into account variability of time and location. Because the toxicity endpoint of interest results from short-term exposure, daily drinking water exposure estimates for multiple OP pesticides and their toxic transformation products were estimated.

Surface water sources of drinking water are more likely to be susceptible to OP contamination than are ground water sources because of the chemical characteristics of OP chemicals. To account for the variability in drinking water exposures, the Agency used a regional approach to address the impacts of regional and localized variability in site, environmental, and management practices that affect pesticide concentrations in water. Within each region, EPA selected locations where OP concentrations in drinking water sources are likely to be of greatest concern based on total OP use and on the vulnerability of the drinking water sources to runoff. These potential high-end exposure scenarios served as regional screens: if OP levels in water from these vulnerable sites are not major contributors to the total regional cumulative exposure, then the Agency can reasonably conclude that drinking water exposures will not be a concern in other, less vulnerable, areas. If drinking water exposure from one or more of these vulnerable sites is a significant contributor to the total cumulative exposure, then additional evaluations may be necessary to characterize the extent of the potential exposure.

The cumulative OP exposure in drinking water must account for OPs that can occur together in time and place. Multi-county level pesticide use information, based on agricultural chemical use surveys, serves as a surrogate for identifying the potential for co-occurring OP uses in the same location. Timing of the applications, along with pesticide persistence and transport characteristics, dictate the relative potential of multiple OPs to

occur together in time. The relative proportions of each OP used in the watershed area are based on the amount applied in a given year (a function of the rate and frequency of application, combined with the crop area treated at that scale); pesticide fate and transport properties that affect the amount of pesticide available at the surface for runoff; the runoff susceptibility of the soil; and the timing, amount, and frequency of rainfall.

3. Updates Since the June 2002 Revised OP Cumulative Risk Assessment

The drinking water exposure assessment for the 2006 update uses the same methods as the 2002 revised OP CRA. Revised inputs that were used to estimate drinking water distributions for the in this update are noted below.

a. Use Revisions

Drinking water exposure distributions for the OP CRA are based on typical application rates, intervals, and timing of application. These use inputs have been derived from surveys of reported use and from regional application timing windows based on pest pressures, cropping dates, and reported applications. Details of this use-related data are documented in the revised OP CRA (US EPA, 2002).

Table I.E-1 provides a list of changes in the OP use inputs for the regional drinking water exposure estimates. Those OPs or uses that have been cancelled or are being phased out are no longer considered as contributors to drinking water exposure. For a few OP pesticides, the maximum label rates and/or frequency of use have been lowered. In those instances where the revised label application rates are less than the typical rates used in the exposure assessment, the revised rates have been used. Where revised label rates remain greater than reported typical rates, those typical rates are still used for the exposure assessment. No use changes occurred in Regions D (Northern Great Plains) or E (Southeast US).

In June 2006, the Agency issued its proposed decision to phase-out all remaining uses of azinphos methyl (AZM) between 2007 and 2010. A Federal Register (FR) notice announcing this decision and soliciting public comments was published on June 9, 2006 (71 FR 33448). The Agency has evaluated OP cumulative risks two ways – with the AZM uses included and excluded. This 2006 Update reflects the termination of these uses. However, for screening purposes, the drinking water exposure assessment included exposures from AZM as a result of the uses that are being phased out. This only impacts exposure estimates in Regions B (Northwest) and C (Southwest). In

neither of these regions did drinking water exposures approach MOEs of 100 or result in cumulative OP exposures exceeding MOEs of 100.

Table I.E-1 Revisions to OP use inputs (application rates, number of applications) as a result of risk management decisions since June 2002.

Region	Pesticide	Use Revision
A (Florida)	Diazinon	Lettuce: changed from 2 ground (soil) applications to 1 at-plant and 1 foliar
		Tomato: reduced number of applications from 2 to 1 (soil applied)
B (Northwest)	Diazinon	Cauliflower: decreased from 2 to 1 application
		Hops: use cancelled
		Cherries: Label rate changed to a maximum of 1 application every other year. Because the percent treated is <50% and the typical rate is < maximum rate, the inputs were not changed.
	Dimethoate	Apples: use cancelled
		Cabbage: use cancelled
	Ethoprop	Snap bean use has been retained. Although label use has been cancelled, a 24(c) label still exists.
	Phosmet	Apples: application rate decreased from 2.24 to 1.5 lb ai/acre
C (Arid/Semi-arid West)	Diazinon	Pears, peaches: Label rate has changed to maximum of 1 application every other year. Because the percent treated is <50% and the typical rate is < maximum rate, the inputs were not changed.
	Dimethoate	Apple: use cancelled
		Grapes: use cancelled
F (Southern Prairie)	Methyl parathion	Cotton: total use rate reduced from 1.92 (3 x 0.64 lb ai/ac) to 0.75 lb ai/acre (2 x 0.375 lb ai/acre)
G (Mid-South)	Dicrotophos	Cotton: total use rate reduced from 0.54 (2 x 0.27 lb ai/ac) to 0.5 lb ai/acre (2 x 0.25 lb ai/acre)
	Methamidophos	Cotton: use cancelled
	Methyl parathion	Cotton: total use rate reduced from 1.56 (4 x 0.39 lb ai/acre) to 0.75 lb ai/acre (2 x 0.375 lb ai/acre)

b. Updated OP Cumulative Distributions

For the regional exposure scenarios, the Agency modeled each OP-crop combination using region-specific usage, application timing, soil, crop, and weather data. The result is a time series of daily OP

concentrations in a drinking water source, spanning multiple years of simulations. EPA re-calculated the daily drinking water concentrations for each of the revised OP uses listed in Table I.E-1.

Each daily concentration is adjusted by the fraction of the watershed that is treated by a particular OP, and the resulting concentration is converted to an index-equivalent concentration using relative potency (RPF) and FQPA safety factors. This normalized output is summed day-by-day to give a single time series of cumulative OP residues. Revisions to the FQPA safety factors for the OP pesticides are documented in the Hazard/Relative Potency Factor section. After incorporating these adjustment factors, the cumulative OP drinking water concentrations, in methamidophos equivalents, decreased in most regions.

Outputs from each OP-crop scenario and subsequent calculations of the combined OP exposures for the regional drinking water exposure estimates can be found in spreadsheets in Appendices II.E.3 through II.E.9.

c. Potential for Oxon Formation

In the 2002 revised OP CRA, the Agency characterized the potential impacts of the conversion of OP pesticides to oxon transformation products during standard drinking water treatment processes. For those OP pesticides that could potentially transform into more toxic oxons, the Agency assumed a complete transformation as a result of drinking water treatment. Based on limited data (documented in the 2002 OP CRA), the Agency assumed that the oxons would persist for a sufficient time to travel through the distribution system. Finally, the Agency assumed that the oxon product would be no more than 10 times more toxic than the parent and consequently applied an additional 10X oxon adjustment factor to the RPF-adjusted concentrations.

Since the 2002 revised OP CRA was published, the Agency has only identified enough data to characterize the relative toxicity differences between the oxon and the parent for three OP pesticides: dimethoate (3X difference between the parent and its oxon, omethoate), chlorpyrifos, and methyl parathion (available data for both indicate that the resulting oxon will be less than 10X more toxic than the parent). For the remaining OP pesticides which form oxons, insufficient data exists to determine a potential oxon adjustment factor. For these pesticides, the Agency used oxon adjustment factors of 10X and 100X to consider upper bound estimates of potential oxon

potency. These adjustment factors were applied to the pesticide concentrations in water.

Although the Agency has limited toxicity information for the oxons, it has reviewed and collected other important data on the potential for oxon formation and oxon persistence. This information, which is summarized in Table I.E-2, comes from a combination of published literature, registrant-submitted studies, US EPA laboratory studies (Office of Research and Development and OPP Biological and Economic Analysis Division laboratories), and monitoring data. The results of recent laboratory bench studies conducted by EPA on the potential for selected OP pesticides to form oxons as a result of chlorination are included in Appendices II.E.1 and II.E.2. These are an addendum to Appendix III.E.4 (Effects of Drinking Water Treatment on Organophosphate Pesticides) in the 2002 OP CRA.

Table I.E-2 Data documenting the potential of OP pesticides to form oxons as a result of drinking water treatment / chlorination processes.

OP	Laboratory Chlorination Studies (1)	Drinking water monitoring data (2)
Azinphos Methyl	Oxon formed (Tierney et al., 2001)	USGS: oxon detected in treated water; parent, oxon detected in untreated waters PDP: Parent not detected; no data for oxon Registrant: analytical problems
Bensulide	Oxon formed, stable for 72 hr (USEPA, 2006a)	No data
Chlorethoxyphos	Oxon formed, stable for 72 hr (USEPA, 2006a):	No data
Chlorpyrifos	Oxon formed (Wu and Laird, 2003; Duirk and Collette, 2005; Tierney et al., 2001)	USGS: Parent detected in untreated waters; no data for oxon PDP: Parent, oxon not detected Registrant: Parent, oxon not detected
Diazinon	Oxon formed (Tierney et al., 2001)	USGS: Parent detected in untreated water; no data for oxon PDP: Parent, oxon found Registrant: Parent not detected; oxon found
Dimethoate	Omethoate is oxon	USGS: Parent found in untreated water; no data for oxon PDP: Parent detected; no data for oxon
Disulfoton	Oxon not formed for parent. Sulfoxide oxon formed but not stable; sulfone oxon formed and stable for 72 hr (USEPA, 2006a,b)	USGS: Parent detected in untreated waters; no data for oxon, sulfone, sulfoxide PDP: Parent, oxon not detected; no data on sulfone, sulfoxide
Malathion	Oxon formed (Tierney et al., 2001)	USGS: oxon detected in treated water; parent detected in untreated

OP	Laboratory Chlorination Studies (1)	Drinking water monitoring data (2)
		waters PDP: Parent detected; oxon not detected Registrant: analytical problems
Methidathion	Oxon formed, stable for 72 hr (USEPA, 2006a)	USGS: Parent detected in untreated waters; no data for oxon PDP: Parent, oxon not detected
Methyl Parathion	Oxon formed, stable for 72 hr (USEPA, 2006a)	USGS: Parent detected in untreated waters; oxon not detected PDP: Parent, oxon not detected
Phorate	Oxon not formed for parent. Sulfoxide oxon formed but not stable; sulfone oxon formed but not stable (USEPA, 2006a,b)	USGS: Parent not detected; no data for oxon, sulfone, sulfoxide PDP: Parent, oxon not detected; no data on sulfone, sulfoxide
Phosmet	Oxon formed, but not stable (USEPA, 2006a)	USGS: No data PDP: Parent not detected; no data for oxon
Phostebupirim	Oxon formed, stable for 72 hr (USEPA, 2006a)	No data
Terbufos	Oxon not formed for parent. Sulfoxide oxon formed but not stable; sulfone oxon not formed (USEPA, 2006a,b)	USGS: Parent not detected; no data for oxon, sulfone, sulfoxide PDP: Parent, oxon not detected; no data on sulfone, sulfoxide

(1) REFERENCES:
Aizawa and Magara ,1992
Duirk and Collette, 2005
Tierney et al. 2001.
USEPA, 2006a.
USEPA, 2006b.
Wu and Laird, 2003

(2) REFERENCES:
USGS, 2001.
PDP, 2005
Tierney et al (2001)

Exposure estimates using oxon adjustment factors are intended to determine the potential extent to which oxon conversion might increase cumulative OP residue exposures in drinking water. The studies summarized in Table I.E-2 are only designed to determine whether oxons form as a result of chlorination and whether they are stable for at least 72 hours after formation. More extensive studies would be required to determine the rates of formation and decline of oxons in treated water. The Agency used this information to determine whether additional information is needed concerning oxon toxicity, extent and rate of oxon formation as a result of standard drinking water treatment, and/or the rate of breakdown of the oxons after formation.

4. Updated OP Cumulative Drinking Water Exposure Estimates

Based on combined OP usage, drinking water intake locations, and pesticide runoff vulnerability, the Agency estimated OP concentrations in drinking water for scenarios that represent a high potential for OP exposure. In the 2002 OP CRA, EPA summarized the individual OP concentrations and the resulting OP cumulative distributions in each of the regional appendices. Table I.E 3 summarizes the upper percentiles of estimated concentrations for each OP included in the regional exposure assessments, and Table I.E 4 summarizes the resulting OP cumulative exposures.

a. Updated Individual OP Distributions

Estimated maximum concentrations of individual OP pesticides in each of the regional high-end exposure scenarios were predominantly in the single- to sub-parts per billion (µg/l) range (Table I.E-3). Estimated exposures, plotted in time series, showed sharp peak concentrations shortly after application and runoff events, quickly declining to concentrations below levels of detection. In all instances, the estimated concentrations of the individual OP pesticides are equivalent to or less than those estimated in the 2002 OP CRA. This reflects the risk management measures that have been put into place (e.g., cancellation of uses, reduced application rates etc).

A comparison of the estimated concentrations to available monitoring data showed that, while estimates of some OP pesticides were less than the highest monitoring detections, estimates of other OP pesticides were on the same order or greater than that found in monitoring studies (USEPA, 2002). In the 2002 OP CRA, EPA concluded that while peak water concentrations for one or more OP pesticides may not be captured in this approach, the impact on the contribution from water to the overall risk assessment is anticipated to be small. None of the updates reported here are expected to change that conclusion.

Table I.E-3 Updated estimated percentile concentrations of individual OP pesticides in each of the regional surface water exposure scenarios (not adjusted for relative potency).

Chemical (1)	Crop/Use	Percentile concentration in µg/l (ppb)				
		Max	99th	95th	90th	80th
Region A (Florida): South FL						
Acephate	Peppers	7.6E-02	6.8E-03	8.5E-04	2.8E-04	8.7E-05
Chlorpyrifos	Corn, citrus	2.0E-01	9.6E-02	4.9E-02	3.3E-02	2.1E-02
Diazinon	Lettuce, tomato	2.9E-02	1.5E-02	8.8E-03	6.1E-03	3.9E-03
Ethoprop	Sugarcane	1.5E+00	5.1E-01	2.5E-01	1.7E-01	9.8E-02
Methamid-	Acephate	9.3E-03	1.7E-03	2.6E-04	8.4E-05	1.6E-05

Chemical (1)	Crop/Use	Percentile concentration in µg/l (ppb)				
		Max	99th	95th	90th	80th
ophos	degradate, tomato					
Phorate	Corn, sugarcane	1.1E+01	7.2E-01	1.8E-02	1.1E-04	5.4E-09
Region B (Northwest): Willamette Valley, OR						
Acephate	Cauliflower, mint, nursery trees/shrubs	5.0E-04	3.6E-04	1.9E-04	7.8E-05	9.7E-06
Azinphos Methyl	Apples, cherries, pears	7.0E-06	2.1E-06	9.5E-07	6.5E-07	4.0E-07
Bensulide	Broccoli, cabbage, cucumbers	4.0E-02	3.2E-02	2.4E-02	2.1E-02	1.8E-02
Chlorpyrifos	Apples, cherries, pears, hazelnut, broccoli, cabbage, onions, sweet corn, mint, Xmas trees, nursery, grass for seed	6.0E-02	2.7E-02	1.6E-02	1.3E-02	9.8E-03
DDVP	Naled degradate	8.2E-04	2.8E-07	2.1E-11	4.9E-12	1.5E-12
Diazinon	Apples, cherries, pears, snap beans, broccoli, cauliflower, onions, peas, cane berries, nursery, blueberry	1.4E-02	9.3E-03	6.2E-03	4.9E-03	3.7E-03
Dimethoate	Cauliflower, peas, cherries, Xmas trees	2.5E-02	2.4E-03	6.4E-04	2.8E-04	1.0E-04
Disulfoton	Broccoli	1.0E-04	8.2E-05	6.1E-05	5.1E-05	4.1E-05
Ethoprop	Beans, snap	7.2E-01	6.6E-01	5.1E-01	4.1E-01	2.8E-01
Malathion	Apples, cherries, blueberry, onions, squash, raspberry	1.5E-02	2.7E-03	9.2E-04	2.6E-04	3.2E-05
Methamid-ophos	Acephate degradate	7.3E-05	1.5E-06	6.4E-09	1.3E-10	2.0E-12
Methidathion	Pears	1.3E-04	5.5E-05	2.8E-05	1.6E-05	5.7E-06
Methyl Parathion	Onions	1.9E-04	5.0E-05	1.9E-05	1.2E-05	5.1E-06
Naled	Broccoli, cauliflower	1.4E-04	3.5E-06	2.6E-10	1.3E-12	7.2E-13
ODM	Cabbage, Xmas trees	7.0E-04	1.4E-04	5.2E-05	3.1E-05	1.6E-05
Phosmet	Apples, cherries, pears	1.3E-03	7.1E-05	1.8E-06	1.8E-08	2.4E-11
Region C (Arid/Semi-Arid West): Central Valley, CA						
Acephate	Legume (dry/ succulent beans), tomato	7.6E-02	3.9E-02	2.4E-02	1.8E-02	1.3E-02
Azinphos Methyl	Almonds, walnuts, apples, pears	3.8E-05	5.7E-06	2.5E-06	1.8E-06	1.3E-06

Chemical (1)	Crop/Use	Percentile concentration in µg/l (ppb)				
		Max	99th	95th	90th	80th
Chlorpyrifos	Alfalfa, almonds, walnuts, apples, pears, peaches, apricots, nectarines, asparagus, corn, grapes, sugarbeet, tomato	1.1E-01	5.2E-02	3.6E-02	2.9E-02	2.2E-02
DDVP	naled degradate, peaches, apricots, nectarines	7.1E-03	8.8E-04	6.2E-04	5.0E-04	3.2E-04
Diazinon	Almonds, walnuts, apples, pears, peaches, apricots, nectarines, broccoli, brassicas, cantaloupe, grapes, tomato	2.3E-01	1.4E-01	8.1E-02	5.6E-02	3.2E-02
Dimethoate	Alfalfa, pears, peaches, apricots, nectarines, broccoli, brassicas, cantaloupe, corn, lebume, tomato	2.5E-01	4.7E-02	1.7E-02	1.2E-02	8.7E-03
Disulfoton	Asparagus	1.3E-02	3.3E-03	2.0E-03	1.4E-03	9.1E-04
Malathion	Alfalfa, asparagus, legume, tomato, corn, grapes	8.6E-03	3.6E-03	1.6E-03	1.1E-03	7.2E-04
Methamid-ophos	Acephate degradate, tomato	1.8E-01	9.7E-02	7.0E-02	5.8E-02	5.0E-02
Methidathion	Apples, pears, Peaches, apricots, nectarines, almonds, walnuts	1.5E-01	6.5E-02	3.5E-02	2.0E-02	8.4E-03
Methyl Parathion	Alfalfa	5.3E-03	2.6E-03	1.4E-03	8.6E-04	1.4E-04
Naled	Almonds, walnuts, peaches, apricots, nectarines, grapes, legumes, sugarbeet	4.3E-03	1.0E-04	2.1E-05	2.0E-06	4.9E-08
ODM	Broccoli, brassicas, cantaloupe, sugarbeet	8.2E-04	4.2E-04	2.5E-04	2.0E-04	1.3E-04
Phorate	Corn, sugarbeet	2.6E-01	1.0E-02	5.2E-04	4.3E-05	3.9E-07
Phosmet	Almonds, walnuts, apples, pears, Peaches, apricots, nectarines, alfalfa	3.2E-02	3.0E-03	6.1E-04	6.3E-05	1.4E-06
Region D (Northern Great Plains): Red River Valley, MN/ND						
Chlorpyrifos	Sugarbeet, wheat	4.3E-01	2.0E-01	1.1E-01	7.8E-02	5.1E-02
Dimethoate	Potato	7.0E-02	3.0E-02	1.5E-02	1.0E-02	6.2E-03
Phorate	Sugar beet	1.8E-02	7.8E-03	3.8E-03	2.4E-03	1.3E-03
Terbufos	Sugar beet	4.2E-01	1.8E-01	9.1E-02	6.1E-02	3.7E-02

Chemical (1)	Crop/Use	Percentile concentration in µg/l (ppb)				
		Max	99th	95th	90th	80th
Region E (Southeast): Eastern NC Coastal Plain						
Acephate	Cotton, peanut, tobacco	1.7E+00	4.3E-02	3.1E-03	7.0E-04	2.1E-05
Chlorpyrifos	Corn, peanut, tobacco	2.6E-01	9.9E-02	5.6E-02	3.8E-02	2.2E-02
Dimethoate	Cotton	7.4E-02	1.2E-02	2.7E-03	1.0E-03	2.3E-04
Disulfoton	Cotton	4.3E-02	2.9E-02	1.7E-02	1.2E-02	7.8E-03
Ethoprop	Tobacco	2.2E-01	1.4E-01	4.8E-02	2.9E-02	1.5E-02
Methamid-ophos	Acephate degradate	2.1E-01	5.2E-03	1.7E-04	9.8E-06	4.5E-08
Phorate	Cotton, peanut	6.6E-01	3.9E-02	1.7E-03	4.7E-05	2.1E-09
Terbufos	Corn	1.5E+00	4.0E-01	1.1E-01	3.9E-02	6.5E-03
Tribufos	Cotton	2.4E-02	1.6E-02	1.1E-02	9.6E-03	7.8E-03
Region F (Southern Prairie): Central Hills, TX						
Acephate	Cotton	1.3E-01	1.2E-02	1.0E-03	1.9E-04	2.0E-06
Chlorpyrifos	Alfalfa, corn, cotton, sorghum	1.3E-01	5.9E-02	2.9E-02	1.9E-02	1.1E-02
Dicrotophos	Cotton	3.9E-02	7.9E-03	2.4E-03	9.3E-04	1.6E-04
Dimethoate	Corn, cotton, wheat	6.5E-02	2.2E-02	7.5E-03	4.6E-03	2.4E-03
Malathion	Cotton	1.5E+00	8.2E-02	3.4E-02	1.5E-02	3.4E-03
Methamid-ophos	Acephate degradate	4.6E-02	8.5E-04	3.1E-05	1.1E-06	1.1E-09
Methyl Parathion	Alfalfa, cotton	3.6E-02	7.2E-03	2.0E-03	1.0E-03	3.0E-04
Phorate	Cotton	4.2E-02	3.8E-03	1.2E-04	2.0E-06	6.7E-10
Phostebu-pirim	Corn	6.9E-02	3.2E-02	1.4E-02	8.9E-03	4.7E-03
Terbufos	Corn	1.4E+00	4.9E-01	1.7E-01	7.9E-02	1.8E-02
Tribufos	Cotton	6.1E-02	3.6E-02	2.3E-02	1.8E-02	1.4E-02
Region G (Mid-South): Mississippi River Valley, MS/LA						
Acephate	Cotton	4.6E+00	7.4E-01	1.1E-01	2.8E-02	1.6E-03
Chlorpyrifos	Corn	3.7E-02	1.6E-02	7.0E-03	3.9E-03	1.8E-03
Dicrotophos	Cotton	1.3E+00	5.9E-01	2.6E-01	1.3E-01	4.3E-02
Dimethoate	Corn, cotton	2.1E-01	6.1E-02	1.3E-02	6.3E-03	1.3E-03
Disulfoton	Cotton	1.3E-02	1.1E-02	6.4E-03	4.9E-03	3.1E-03
Malathion	Cotton	1.3E+01	1.8E+00	4.2E-01	2.5E-01	8.5E-02
Methamid-ophos	Acephate degradate	5.7E-01	7.7E-02	4.5E-03	2.8E-04	1.6E-06
Methyl Parathion	Cotton, soybean	1.8E-01	7.5E-02	4.1E-02	2.2E-02	7.5E-03
Phorate	Cotton	5.6E-01	8.7E-02	4.2E-03	1.1E-04	8.8E-08
Phostebu-pirim	Corn	3.6E-02	1.5E-02	7.3E-03	4.5E-03	2.5E-03
Profenofos	Cotton	1.8E-01	2.7E-02	3.8E-03	9.7E-04	9.1E-05
Terbufos	Corn	1.0E+00	3.5E-01	1.2E-01	6.8E-02	2.1E-02
Tribufos	Cotton	3.3E-01	2.2E-01	1.7E-01	1.2E-01	7.6E-02

(1) Estimated concentrations for disulfoton, phorate, and terbufos reflect combined residues of the parent and its sulfoxide and sulfone transformation products.

b. Updated Cumulative OP Distributions

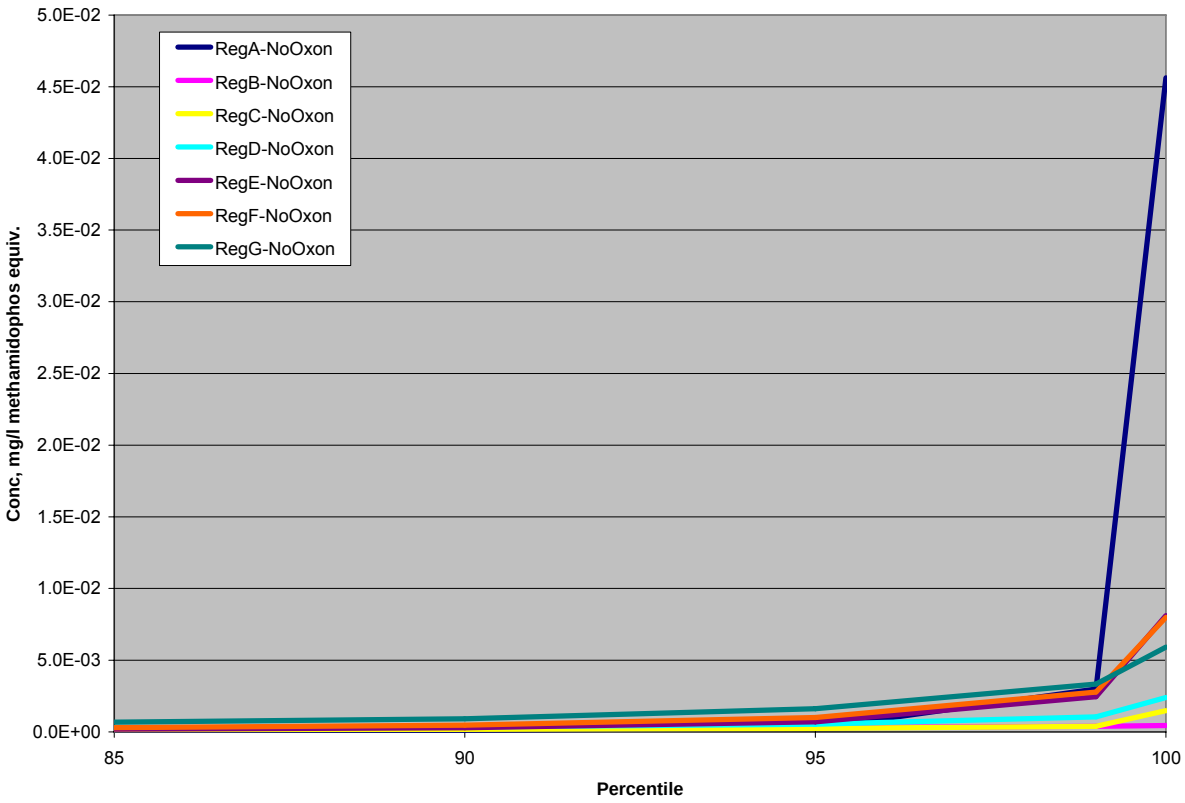
Region A (Florida) had the highest cumulative peak concentrations above the 99th percentile, while peak concentrations in Regions E (Southeast), F (Southern Prairie), and G (Mid-South/ lower Mississippi River Valley) were roughly 6 to 8 times lower (Table I.E-4 and Figure I.E-1). All four of these regions were similar in concentration at the 99th percentile. Estimated peak concentrations for the remaining three regions – B (Northwest), C (Southwest/ Central Valley), and D (Northern Great Plains) – were approximately an order of magnitude lower than the other regions.

Table I.E-4 Percentile summaries of OP cumulative distribution (mg/l in methamidophos equivalents) from 24-36 years of simulation in each of the cumulative regions.

Percentile	Reg A	Reg B	Reg C	Reg D	Reg E	Reg F	Reg G
Max	4.6E-02	4.5E-04	1.5E-03	2.4E-03	8.1E-03	8.0E-03	5.9E-03
99	3.0E-03	4.0E-04	4.0E-04	1.1E-03	2.5E-03	2.8E-03	3.3E-03
95	2.6E-04	3.1E-04	2.4E-04	5.3E-04	7.0E-04	1.0E-03	1.6E-03
90	1.2E-04	2.5E-04	1.9E-04	3.6E-04	2.9E-04	4.8E-04	9.1E-04
80	6.4E-05	1.7E-04	1.4E-04	2.2E-04	8.8E-05	1.2E-04	4.4E-04
75	5.2E-05	1.5E-04	1.2E-04	1.8E-04	5.8E-05	6.5E-05	3.1E-04
70	4.4E-05	1.4E-04	1.1E-04	1.5E-04	4.3E-05	3.7E-05	2.1E-04
65	3.7E-05	1.3E-04	1.0E-04	1.2E-04	3.3E-05	2.3E-05	1.5E-04
60	3.2E-05	1.2E-04	9.3E-05	1.1E-04	2.7E-05	1.7E-05	1.2E-04
50	2.4E-05	9.9E-05	7.9E-05	8.2E-05	1.9E-05	1.1E-05	6.3E-05
Major OP driver(s)	phorate (1)	ethoprop	metha-midophos, methida-thion	terbufos (1)	terbufos (1)	terbufos (1)	dicroto-phos

(1) Includes the sulfone and sulfoxide transformation products that form in the environment.

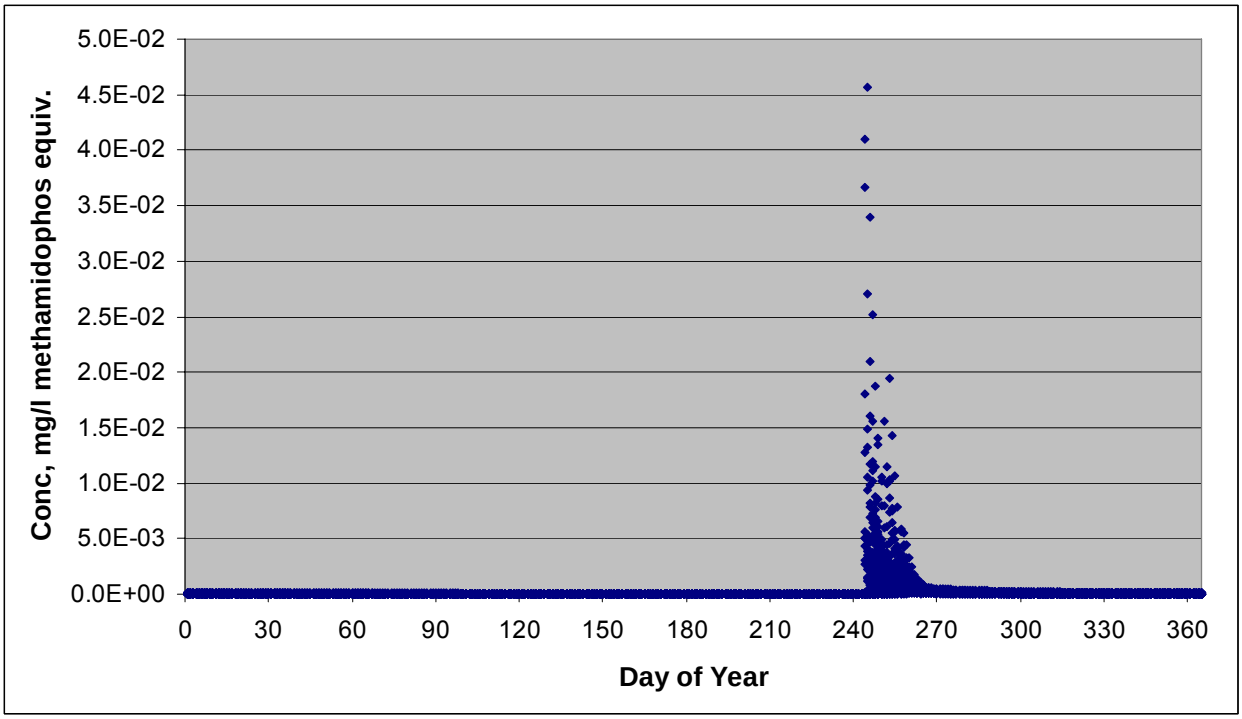
Figure I.E-1 Frequency Distribution of Each of the Regional OP Cumulative Drinking Water Exposures.



In the Region A (Florida) scenario, the temporal and spatial extent of potential high OP exposure is limited. The seasonal duration of exposure in the south Florida scenario is relatively short (Figure I.E 2) and is associated with phorate and ethoprop use on sugarcane. The cumulative peak is driven largely by phorate and its sulfoxide and sulfone residues which form in the environment. The peak seen in Figure I.E 2 assumes that the applications occur on the same day every year. Year-to-year peaks are likely to vary in timing because the actual dates of application may vary within an optimal window of application from year to year. Thus, the spread in yearly peaks may be broader than shown in the figure.

As the Agency noted in the 2002 OP CRA, existing monitoring data from NAWQA and from the South Florida Water Management District (SFWMD) did not include the sulfoxide and sulfone residues of phorate, precluding modeling-monitoring comparisons for the estimated exposures. Thus, it is difficult to evaluate modeled estimates against measured concentrations of total phorate residues.

Figure I.E-2 Variations in yearly pattern of cumulative OP concentrations in water in the Florida Region (35 years of varying weather patterns).



The majority of Florida's drinking water is drawn from groundwater rather than from surface water sources (see II.A. Regional Assessment for Region A – Florida in the 2002 OP CRA). The surface water intakes found in south Florida are represented by the exposure scenario for Region A. Drainage canals from sugarcane fields are not used directly for drinking water, but water from drainage canals eventually feed water bodies used in southern Florida for drinking water supply. Sugarcane is grown south of Lake Okeechobee in the Everglades Agricultural Area (EAA), and to the east into Palm Beach County. Three community water systems (CWS) draw from the southern end of Lake Okeechobee, and the city of West Palm Beach draws water from Clear Lake, which is fed in part by drainage water from the EAA.

Although the drinking water treatment studies referenced in Table I.E 2 and Appendix II.E.1 were designed only to determine the potential for oxon formation as a result of chlorination, they do suggest that the phorate residues (parent plus transformation products) are not likely to be stable as a result of chlorination. Thus, the overall phorate levels in drinking water in south Florida are likely to be much lower than estimated here.

5. Characterizing the Impacts of Potential Oxon Formation on OP Cumulative Distributions in Drinking Water

For the OP pesticides, information on the potential to form oxons as a result of chlorination and on differential toxicities between parent and oxon are not sufficient to make quantitative adjustments to the cumulative exposure estimates. Instead, the Agency conducted a qualitative assessment to determine whether additional information is needed on the relative potency of the oxons as well as the extent and rate of formation and decline of oxon transformation products as a result of chlorination.

a. Estimating Oxon Concentrations from Individual OP Pesticides

In estimating potential oxon impacts, the Agency assumed that any transformation as a result of chlorination results in complete conversion to the oxon. If the transformation is less than complete and if non-toxic products are also formed, this assumption will overestimate the ultimate drinking water exposure. While limited information suggests that some OP parents may be transformed and removed from treated drinking water, sufficient information is not available to quantify this process for all OP pesticides. Thus, the Agency did not assume that any of the other OP parent pesticides would be removed. Except for phosmet, phorate sulfone, and the sulfoxides of disulfoton, phorate and terbufos, available laboratory data indicate that oxons formed as a result of treatment are stable for at least 72 hours, sufficient time to move through the distribution system.

The resulting estimates of oxon residues in drinking water represent an upper bound of the potential oxon levels that may actually occur in drinking water. As mentioned earlier, the studies referenced in Table I.E 2 were not designed to determine definitively what percentage of the parent OP might convert to the oxon. While this percentage is likely to vary depending on treatment conditions, anything less than 100% conversion will result in lower oxon levels than estimated. Similarly, the Agency's assumption that the oxons remain stable after they are formed is an upper bound estimate of the extent that the oxons degrade at any appreciable rate between the time they are formed to when they are distributed at the tap.

In the 2002 OP CRA, EPA assumed that disulfoton, phorate, terbufos and their sulfone and sulfoxide transformation products would not form oxons as a result of treatment. However, recently completed laboratory bench studies conducted by EPA (Appendices II.E.1 and II.E.2) show that the sulfone transformation product of disulfoton forms an oxon that is stable. The revised characterization includes this as a

part of the impacts of potential oxon formation on cumulative OP exposures from drinking water.

b. Potential Oxon Impacts on Cumulative OP Distributions

As noted, EPA applied an oxon adjustment factor of 3X for dimethoate and 10X for chlorpyrifos and methyl parathion based on available studies. For the remaining OP pesticides which form oxons, the Agency used oxon adjustment factors of 10X and 100X to consider upper bound estimates of potential oxon potency.

With a 10X adjustment factor, increases in estimated peak concentrations (above the 95-99th percentiles) ranged from minimal for Region A (Florida), which had the highest peak concentrations, to a 3-5X increase for Region C (Southwest/California Central Valley), which had one of the lowest peak concentrations (Table I.E-5). For most regions, peak concentrations increased by less than 25-50%. The relative ranking of the regional distributions remained the same as shown in Figure I.E-1.

With a 100X adjustment factor, peak concentrations in Regions B, C, E, F, and G shifted upwards in relation to that of Region A. However, only the distribution for Region C increased (by 30 to 50X) to the extent that it surpassed the distribution of Region A (Figure I.E-3).

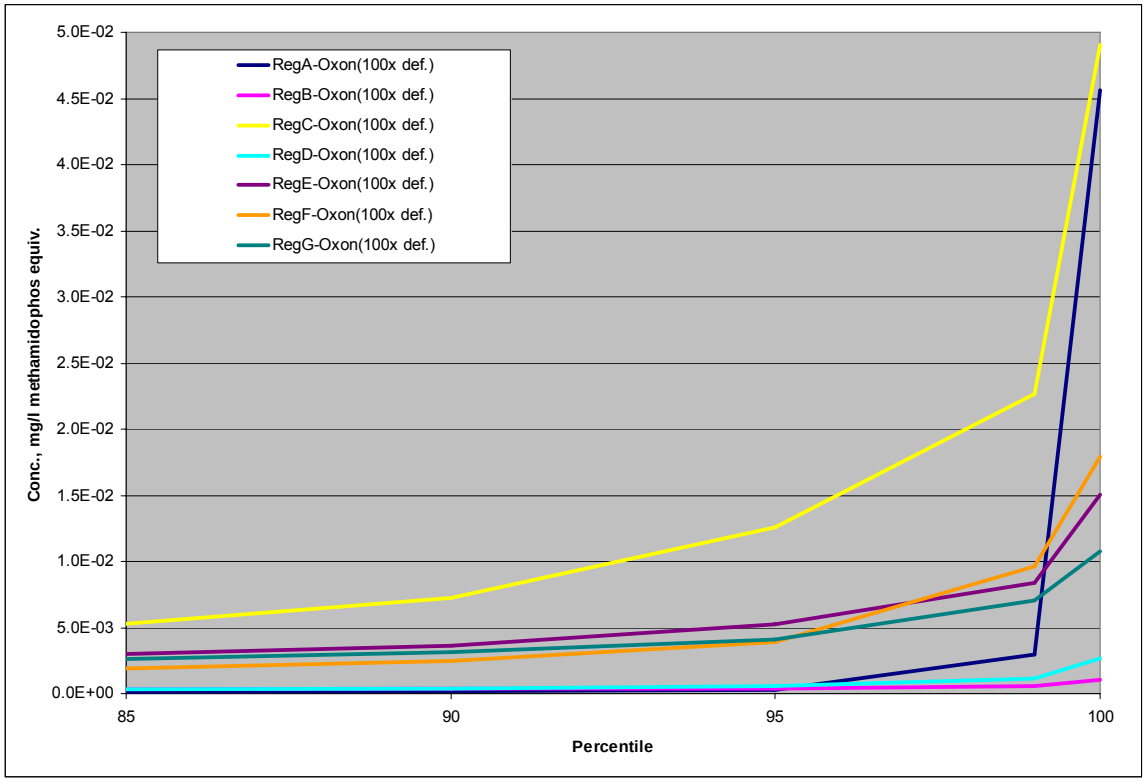
Table I.E-5 Comparison of the effect of potential oxon adjustment factors on the OP cumulative distributions for each of the regional scenarios.

Oxon adjustment factor (1)	Percentile concentration (mg/l in methamidophos equivalents)					Oxon formers
	100	99	95	90	80	
Region A (Florida - South Florida)						
None	4.6E-02	3.0E-03	2.6E-04	1.2E-04	6.4E-05	chlorpyrifos, diazinon
10X	4.6E-02	3.0E-03	2.7E-04	1.4E-04	8.0E-05	
% increase	0.02%	0.05%	4.4%	16.6%	26.0%	
100X	4.6E-02	3.0E-03	3.1E-04	1.9E-04	1.2E-04	
% increase	0.02%	0.07%	19.2%	58.0%	91.1%	
Region B (Northwest - Willamette Valley)						
None	4.5E-04	4.0E-04	3.1E-04	2.5E-04	1.7E-04	azinphos methyl, bensulide, chlorpyrifos, diazinon, dimethoate, disulfoton sulfone, malalathion, methidathion
10X	5.3E-04	4.2E-04	3.2E-04	2.6E-04	1.8E-04	
% increase	18.0%	4.8%	4.6%	4.5%	5.2%	
100X	1.0E-03	5.7E-04	4.2E-04	3.4E-04	2.7E-04	
% increase	128%	42.1%	36.7%	38.8%	61.8%	
Region C (Arid/Semi-Arid West - CA Central Valley)						
None	1.5E-03	4.0E-04	2.4E-04	1.9E-04	1.4E-04	azinphos methyl, chlorpyrifos, diazinon, dimethoate, disulfoton sulfone, malathion,
10X	5.0E-03	2.4E-03	1.4E-03	8.3E-04	4.3E-04	
% increase	240%	507%	463%	343%	214%	
100X	4.9E-02	2.3E-02	1.3E-02	7.3E-03	3.4E-03	

Oxon adjustment factor (1)	Percentile concentration (mg/l in methamidophos equivalents) 100	99	95	90	80	Oxon formers
% increase	3221%	5629%	5079%	3769%	2393%	methidathion, methyl parathion
Region D (Northern Great Plains - Red River Valley)						
None	2.4E-03	1.1E-03	5.3E-04	3.5E-04	2.2E-04	chlorpyrifos, dimethoate
10X	2.7E-03	1.2E-03	5.9E-04	4.0E-04	2.5E-04	
% increase	11.6%	11.5%	11.5%	11.7%	14.0%	
100X	2.7E-03	1.2E-03	5.9E-04	4.0E-04	2.5E-04	
% increase	11.6%	11.5%	11.5%	11.7%	14.0%	
Region E (Southeast - NC Coastal Plain)						
None	8.1E-03	2.5E-03	7.0E-04	2.9E-04	8.8E-05	chlorpyrifos, dimethoate, disulfoton sulfone
10X	8.2E-03	2.8E-03	1.1E-03	6.3E-04	3.4E-04	
% increase	0.7%	12.4%	50.5%	117%	286%	
100X	1.5E-02	8.4E-03	5.2E-03	3.6E-03	2.3E-03	
% increase	85.0%	242%	291%	425%	977%	
Region F (Southern Prairie - central TX)						
None	8.0E-03	2.8E-03	1.0E-03	4.8E-04	1.2E-04	chlorpyrifos, dimethoate, malathion, methyl parathion, phosetebupirim
10X	8.7E-03	3.2E-03	1.3E-03	7.0E-04	2.6E-04	
% increase	8.8%	15.7%	26.4%	47.3%	119%	
100X	1.8E-02	9.6E-03	3.9E-03	2.5E-03	1.3E-03	
% increase	124%	248%	291%	425%	977%	
Region G (Mid-south - LA-MS)						
None	5.9E-03	3.3E-03	1.6E-03	9.1E-04	4.4E-04	chlorpyrifos, dimethoate, disulfoton sulfone, malathion, methyl parathion, phosetebupirim
10X	6.1E-03	3.7E-03	1.8E-03	1.1E-03	6.8E-04	
% increase	2.3%	9.9%	14.0%	24.0%	53.2%	
100X	1.1E-02	7.0E-03	4.1E-03	3.1E-03	2.1E-03	
% increase	81.7%	110%	153%	242%	379%	

(1) Oxon adjustment factors:
None – no adjustments made
10X – 3X applied for dimethoate, 10X for all other oxon formers
100X – 3X applied for dimethoate, 10X for chlorpyrifos and methyl parathion, 100X applied for all other oxon formers

Figure I.E-3 Frequency Distribution of Each of the Regional OP Cumulative Drinking Water Exposures, Including Oxon Adjustment Factors (100X default).



The exposure scenario for Region C includes a number of oxon formers which had peak concentrations within two orders of magnitude of the cumulative peaks (chlorpyrifos, diazinon, dimethoate, methidathion, methyl parathion). With a 10X oxon adjustment factor, methadathion peak concentrations shift to become a major contributor, producing a 3-5X increase in cumulative concentrations for the region. If a 100X oxon adjustment factor is used, methidathion oxon becomes the dominant contributor to the OP cumulative exposure (Figures I.E-4 and I.E-5).

Figure I.E-4 Contributions of individual OP pesticides to the RPF-adjusted cumulative load for Region C (CA Central Valley) with no oxon adjustment factor.

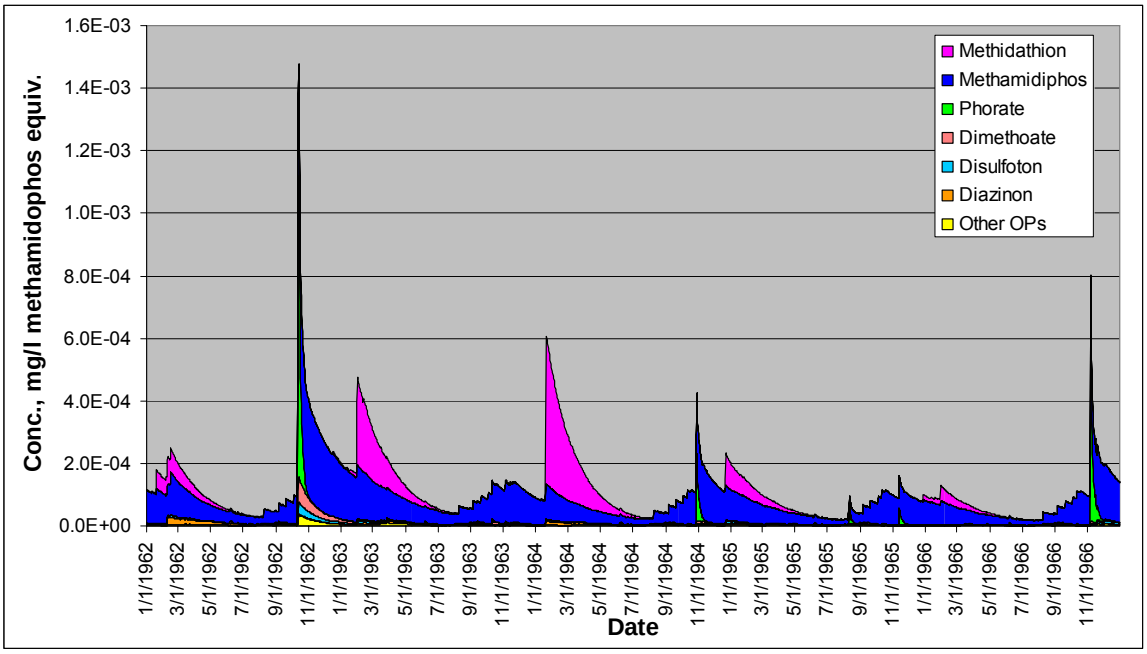
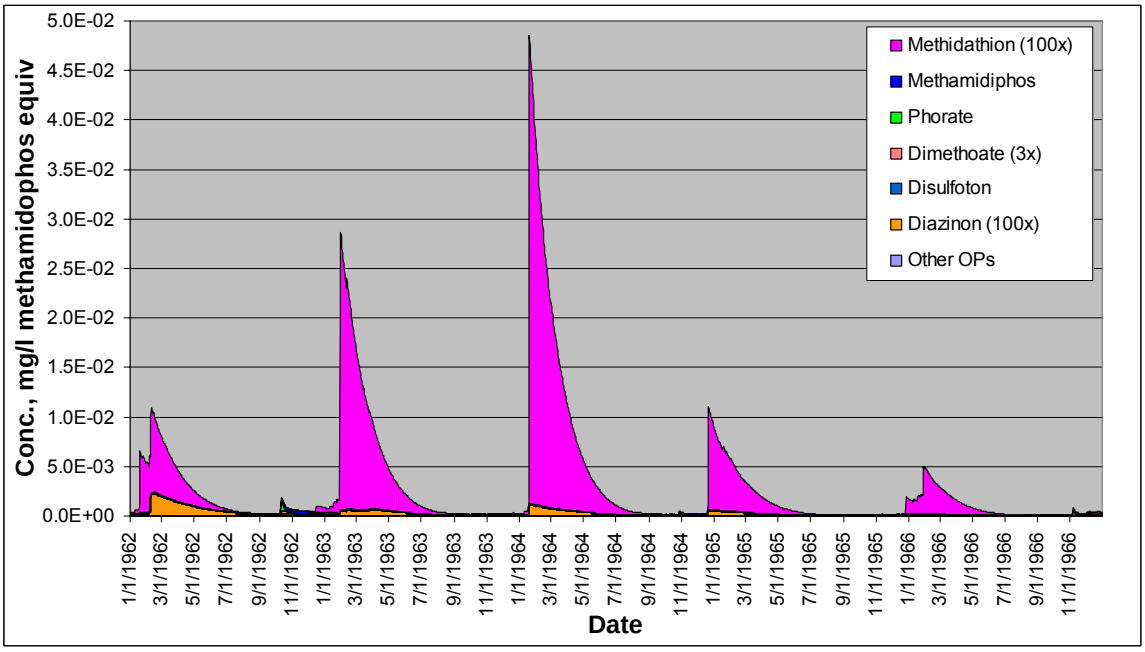


Figure I.E-5 Contributions of individual OP pesticides to the RPF-adjusted cumulative load for Region C (CA Central Valley) with a default 100X oxon adjustment factor.



Although the Agency believes that the assumptions applied to this oxon characterization are conservative and that actual exposures are expected to be less than estimated, the data are insufficient to make a quantitative determination at this point. The uncertainty in the exposure estimates for the oxons in this region (in particular, for methidathion oxon) is addressed in the risk characterization section (I.G) and in Appendix II.G.3.

F. The Multi-Pathway Cumulative Assessment

1. Introduction

The previous sections of this document have described the development of the major components of the risk assessment. They present 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 considered. 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 and risks associated with OP pesticides. The purpose of this section is to explain the concepts used to accumulate risk from each pathway into a total risk estimate, summarize some of the major findings, and provide a basis for understanding the graphical temporal exposure profiles that are provided in the Appendices. It is these graphs that summarize many of the aggregate/cumulative results of this assessment.

OPP used a probabilistic assessment to capture the full range of exposure possibilities from all sources analyzed. The intent was to produce an estimate of risk that is as realistic as possible. OPP believes that the assessment reflects the full range of likely exposures for consideration in a regulatory context and avoids developing extreme exposure estimates based upon the combination of exposure scenarios and assumptions that are not reasonable.

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 and nature. As described in section I.B of this OP Cumulative update, the RPF method was used to address the issue of combining toxic responses from OPs with varying potencies with respect to inhibiting 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 based on response by route-specific dosing, and do not support estimating delivered dose to the target tissue (which would be considered the ideal). OPP addressed this issue by comparing route-specific exposures to route-specific points of departure (PoD) to produce unitless margins of exposure for each route. Thus, each exposure route is associated with an MOE for that route. A total (or combined) MOE was calculated by taking the inverse of the MOE for each route, adding these together, and then taking the inverse of that sum. This process was used to produce a distribution of daily estimates of MOEs for the subpopulation

of concern that reflects regional and seasonal variation[18] in the patterns of exposure that are likely to occur throughout the US across the year. This method has been standard practice for developing total MOE estimates for aggregate and cumulative assessments and is further described in OPP's 2001 Aggregate guidance document
http://www.epa.gov/pesticides/trac/science/aggregate.pdf

3. Framing the Population-Based Assessment

OPP used the above-described methodologies 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 used the Calendex software to develop the distributions and resulting MOEs. Calendex permits incorporation of time-course information with regard to residential uses of pesticides and exposures through drinking water, but does not permit specific allowance for regional variability. As described in section I.E of this document, OPP addressed this issue by focusing on and developing separate assessments for regional locations that represent what is likely to be the most vulnerable drinking water sources in high organophosphorus use areas. Based on a comparison of estimated drinking water exposures from surface- and ground-water sources in seven regions as part of the OP CRA 2006 Update, OPP selected drinking water exposures representing what have been determined to be the three most vulnerable areas – Florida, Mid-South, and the Arid/Semi-Arid West Regions – for the multi-pathway assessment. OP exposures in drinking water from the remaining parts of the country are expected to be substantially lower than from these three sites.[19]

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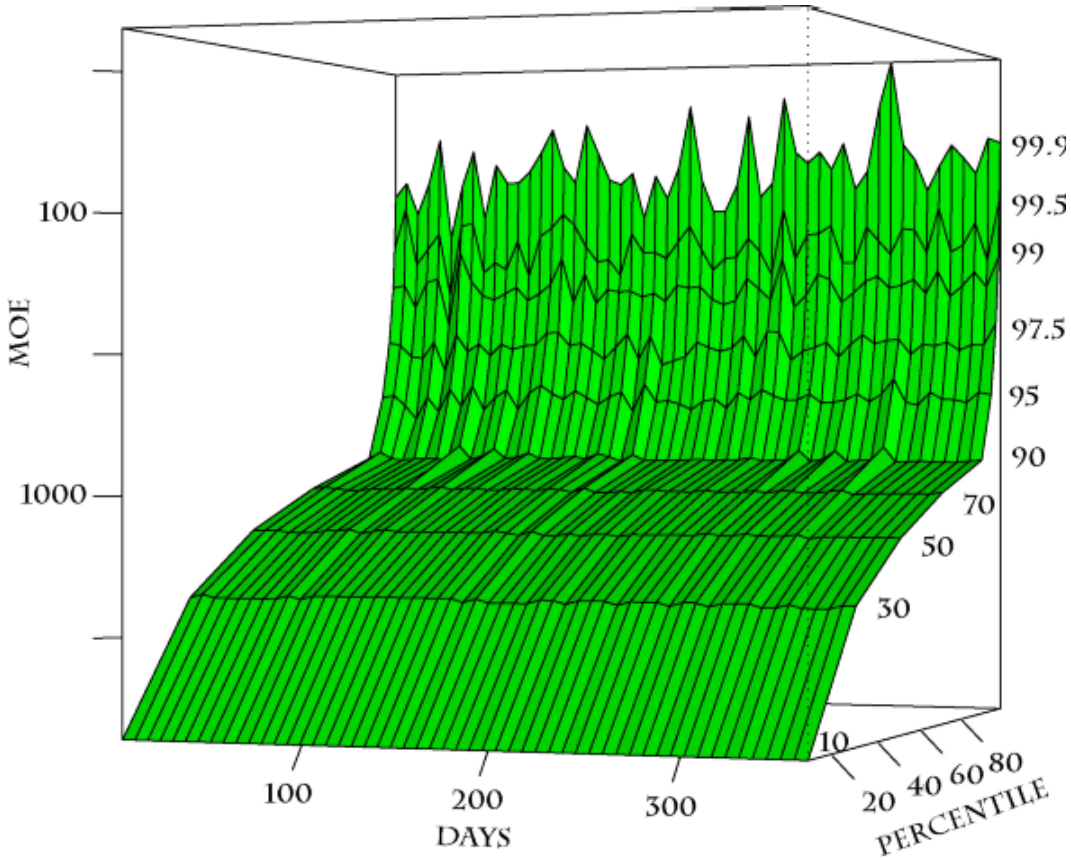
[18] Note that seasonal variation was only considered for the residential and drinking water pathways. No seasonal variation was considered for the food pathway.

[19] OPP recognizes that there is potential for stable oxons to form in treated drinking water as a result of standard drinking water treatment practices and that available studies confirm the potential for 10 OPs to form these stable oxons. These studies, however, do not provide enough information to quantify the rate of formation and decline of the oxons in treated water and limited information is available on the relative toxicity for only three of the oxons. For the remaining OP pesticides, EPA used 10X and 100X adjustment factors to bracket the potential toxicity differences between the parent compounds and their oxons. Although the Agency believes that the assumptions applied to this oxon characterization are conservative and that actual exposures are expected to be less than estimated, the data are insufficient to make a quantitative determination at this point. Nevertheless, OPP used these adjustment factors both to identify those regions which are potentially vulnerable (here, the Florida, Mid-South, and the Arid/Semi-Arid West Regions) and to develop exposure and risk assessments; for this latter goal, separate exposure and risk estimates were developed for each region based on the 1x, 10x, and 100x adjustment factors.

To generate a daily distribution of exposure for the subpopulation of interest, a consumption record is selected from the CSFII that corresponds to the age group of interest. Calendex uses this consumption record to estimate OP exposure from food by randomly assigning a residue value for each food included. After multiplying each amount of food consumed by its selected residue value, the total exposure for this individual from food is summed. 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; not likely in January). If the scenario is assigned a "yes" answer, then the appropriate values defining the exposure are selected from the many distributions of input parameters for residential exposure scenarios. Dermal, oral and inhalation exposures are calculated for all selected residential scenarios. A drinking water value taken from the estimated distribution of water residues 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 to build a distribution of exposures for January 1. This process is repeated for January 2, January 3 and so forth across the same 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. A hypothetical 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 that has less than or equal exposure. For example, 80 % of the population has an exposure level that is equal to or less than the 80th percentile.

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



4. Interpreting the Outputs

The results of the final assessment are presented in graphical form in the appendices. They 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 99.9th percentile of exposure for the population. A slice through the surface parallel to the **xy** plane at the 99th percentile would look like the plots presented in Appendix III. These plots present the potential total MOE for the population exposed to OPs by 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 percentiles of exposure may also be of interest.

OPP will use the changes in graphical presentations of data such as these to evaluate the significance of various sources of exposure, considering both the percentile at which the exposure becomes significant and the duration over which the exposure route and source remain dominant in the risk assessment results.

5. Attributes of the Revised Organophosphorus Cumulative Risk Assessment

The current preliminary assessment focuses on estimating the potential risk from exposure to more than 30 organophosphorus pesticides and metabolites in food and drinking water and from residential uses. The assessment is limited in geographic scope to the Southern area of the U.S. This limitation was placed on the assessment to ensure that the water and residential components of the assessment would reflect what a coherent set of pesticide uses are likely to exist. Understanding the likelihood of co-occurrence of pesticide uses is critical to developing a reasonable estimate of total cumulative risk. In the absence of direct measures of co-occurrence, overlapping exposures must be extrapolated from use data.

As indicated previously in this report, a PoD was used for the oral component of the total cumulative risk assessment. The estimated BMD_{10} (0.08 mg/kg body wt/day) for brain AChE inhibition by the index compound (methamidophos) was used. The inhalation and dermal components of the assessment were compared to BMD_{10}'s of 0.39 and 2.12 mg/kg body wt/day, respectively.

Integrated cumulated risk assessments were conducted for the following age groups: Infants less than 1 year, Children 1-2 years, Children 3-5 years, Children 6-12, Youth 13-19 years, Females 13-49 years, Adults 20-49 years, and Adults 50+ years of age. These eight groups were chosen to emphasize the effects of differences in behavior and food consumption patterns on estimating the risk from exposure to pesticides; these are the standard age groups used by OPP in its dietary assessments. The assessments reflect the same assumptions about use scenarios, timing of exposures and exposures to pesticides in food and water as used in the previous pathway specific assessments. An entire year of exposure is simulated. Five different water scenarios from the three southern regions were matched with a residential scenario that used southern application timing patterns. One water scenario simulated surface water sources in the Arid/Semiarid West Region, one scenario represented a surface water source in the Florida region, and a third represented Mid-South scenario. An additional two scenarios for the Arid/Semiarid West region provided a sensitivity analysis with respect to oxon toxicity.

The food component of the cumulative risk assessment contains as many commodities as could reasonably be extrapolated from the available PDP and FDA monitoring data. This component of the assessment is regarded as highly refined and reflective of exposures likely to be encountered by the U.S. population. Because data on residential exposure are more limited, the residential component of the assessment was also designed to reflect some overestimation bias to ensure that risk from these sources of exposure were not likely to be underestimated. The water components of the assessment focused on what OPP believes are the most vulnerable drinking water sources. While the estimated drinking water concentrations are reasonable reflections of actual exposures in those particular areas, the rest of the country not presented in the figures is expected to have substantially lower OP residue levels in its drinking water.

As discussed earlier, exposure estimates are specific to the regions discussed; they take into account region-specific water and residential use practices and cannot – as a general matter – be necessarily extrapolated to different regions[20]. Further description of these uncertainties and analyses is described in Section D of this document. OPP notes that OP drinking water concentrations in the much of the rest of the U.S. would be expected to be substantially lower such that exposure through drinking water would be a negligible.

Estimates of cumulative risk from organophosphorus pesticide associated with exposure through foods, drinking water, and residential uses are presented in Appendices III.A-E for Infants less than 1 year, Children 1-2 years, Children 3-5 years, Children 6-12, Youth 13-19 years, Females 13-49 years, Adults 20-49 years, and Adults 50+ years of age. The contributions of each of the major routes of exposure and the likely sources of those exposures are discussed in previous sections of this updated assessment. Graphical presentations are limited to the 95th, 99th, and 99.9th percentiles because these percentiles capture the higher end of exposure, which has traditionally been of most interest to the Agency.

The discussion below highlights and summarizes the critical aspects of a number of these temporal profile plots described above. The discussion centers on the region associated with the worst case water scenario (Region A) and residential scenarios and considers various features of the plots for the 95th, 99th, and 99.9th percentiles of exposure.

[20] OPP created a region that comprised all Region A residential uses plus all other OP residential uses that were previously excluded from Region A. This region is referred to as “Region X” and provides a worst case combination of all OP residential uses. Additionally, for each residential scenario in Region X, worst-case assumptions regarding percent of households treated and application frequency were used.

The focus of this discussion is on the MOEs associated with the 21 day rolling average mode of analysis since (as described in Section I.B. of this document), this is the analysis which best "matches" the relevant toxicological endpoint and is thus the most appropriate analysis for consideration.

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REGION A Analyses:

a. 21-day rolling average, children 1-2 years, Region A, no oxon Florida

The results of the total cumulative assessment for Children 1-2 years using the BMD_{10} of the index chemical (methamidophos) for the PoD are presented in Appendix III.A Temporal Exposure Profile Plot for Florida Water in Figure III.A 4, Figure III A 5, and Figure III A 6

95th Percentile

As shown in Figure III.A 4, the significant source of pesticide risk from exposure to pesticides at this percentile of exposure is through the water pathway with total MOEs ranging from 220 to approximately 440. Drinking water shows a spike for a period of less than 30 days, which is dominated by the sulfoxide and sulfone products of phorate, where the lowest MOE reached was 360 and averaged around an MOE of 11,000. Food MOEs are 550. The oral non-dietary component of the assessment was stable across time with an MOE that is generally near 2,000 across the year. Inhalation and dermal exposures that are associated with residential use are typically rather low at this percentile with their MOEs in the 2,000 and 4,000 ranges, respectively.

99th Percentile

As shown in Figure III.A 5, the total MOEs ranged from 120 to 220. At this percentile, the daily MOE values from drinking water sources ranged from 160 to ca. 55,000 and comprise the major source for total exposure with the lowest MOEs occurring for about three weeks beginning mid-August from the sulfoxide and sulfone products of phorate (uses on sugarcane and sweet corn). Food exposures were somewhat lower than this high period of drinking water exposure with consistent MOEs of 250. MOEs from oral non-dietary ingestion which are associated with residential use (i.e., hand-to-mouth) were generally not a very large contributor to the overall exposure. The MOEs for oral non-dietary exposure pathway ranged from ca. 800 to greater than 2,000. MOEs

associated with the dermal route are generally greater than 23,000 but as low as ca. 2,200. Inhalation exposure resulted in MOEs between 320 and 420.

99.9th Percentile

As shown in Figure III.A 6, at the 99.9th percentile, the total cumulative risk (all pathways) is close to 100 for most of the year but for a short time as low as 61 for this age group. Nearly all of the estimated exposure came through the oral route where food was the driver with water contributing substantially for only a short period of time – a couple weeks near Day 230 where the MOE dipped noticeably below 100. Food contributed most significantly with an MOE of 110. Oral non-dietary exposure (hand-to-mouth) resulted in MOEs remaining consistent through the year between ca 790 and nearly 2,000. Dermal MOEs go down to ~ 150 from day 186 to day 243 (from post-application exposure to trichlorfon lawn treatment) and are greater than 1,000 during the first 100 days of the year and remained near 1,000 after day 250. Inhalation MOEs were consistently greater than ca. 180 throughout the year (from exposure to DDVP pest strips.)

b. 21-day rolling average, children 3-5 years, Region A, no oxon Florida

The results of the total cumulative assessment for Children 3-5 years using the BMD_{10} of the index chemical (methamidophos) for the PoD are presented in Appendix III.A Temporal Exposure Profile Plot for Florida Water in Figure III.A 7, Figure III.A 8, and Figure III.A 9.

95th Percentile

As shown in Figure III.A 7, the significant source of pesticide risk from exposure to pesticides at this percentile of exposure is through the food pathway with total MOEs ranging from 250 to approximately 540. Food MOEs remain at 670. The oral non-dietary component of the assessment varied across time with an MOE that never dropped below 900 across the year. Inhalation and dermal exposures that are associated with residential use are typically rather low at this percentile with their MOEs greater than 2,000 and 6,000, respectively. Drinking water shows a spike for a period of less than 30 days where the lowest MOE reached was 400 due to sulfoxide and sulfone products of phorate, but averaged around an MOE of 10,000 for most of the year.

99th Percentile

As shown in Figure III.A 8, the daily total MOEs ranged from 130 to 250. At this percentile, the daily MOE values from drinking water sources ranged from 185 to ca. 52,000 and comprise the major source for total exposure with the lowest MOEs occurring for about three weeks beginning mid-August. Food exposures were somewhat lower than this high period of drinking water exposure with consistent MOEs at 300. MOEs from oral non-dietary ingestion which are associated with residential use (i.e., hand-to-mouth) were generally not a very large contributor to the overall exposure. The MOEs for the oral non-dietary exposure pathway ranged from ca. 900 to greater than 2,000. MOEs associated with the dermal route are generally greater than 10,000 but as low as ca. 3,000. Inhalation exposure resulted in MOEs between 440 and 530.

99.9th Percentile

As shown in Figure III.A 9, at the 99.9th percentile, the total cumulative risk (all pathways) was as low as 61 for this age group. Nearly all of the estimated exposure came through the oral route that included significant contributions from oral non-dietary, drinking water and food pathways. Food contributed most significantly to this MOE except when the MOEs dipped below 99 at which time the water contribution spiked to an MOE of 60. Oral non-dietary exposure (hand-to-mouth) resulted in MOEs remaining consistent through the year between ca 900 and 2,300. Dermal MOEs go down to 260 (due to post-application exposure to trichlorfon lawn treatment) from day 186 to day 243 and are greater than 1,000 during the first 100 days of the year and remained near 1,000 after day 250. Inhalation MOEs were greater than ca. 200 (due to inhalation exposure from the residential uses of DDVP).

c. 21-day rolling average, adults 20-49 years, Region A, no oxon Florida

The results of the total cumulative assessment for adults 20-49 years using the BMD_{10} of the index chemical (methamidophos) for the PoD are presented in Appendix III.A. Temporal Exposure Profile Plot for Florida Water in Figure III.A16, Figure III.A 17, and Figure III.A 18.

95th Percentile

As shown in Figure III.A 16, the significant source of pesticide risk from exposure to pesticides at this percentile of

exposure is through the food pathway with total MOEs as low as 430 with an average MOE of 940. Food MOEs stayed near 820. Inhalation and dermal exposures that are associated with residential use are typically rather low at this percentile with their MOEs greater than 20,000 and 3,600, respectively. Drinking water shows a spike for a period of less than 30 days where the lowest MOE reached was ca 600 and averaged around an MOE of 12,000.

99th Percentile

As shown in Figure III.A 17, the daily total MOEs ranged from 220 to 510. At this percentile, the daily MOE values from drinking water sources ranged from 270 to ca. 57,000 and comprise the major source for total exposure with the lowest MOEs occurring for about three weeks beginning mid-August. Food exposures have consistent MOEs averaging 610. MOE's associated with the dermal route are generally greater than 12000. Inhalation exposure resulted in MOEs between ca 840 and 980.

99.9th Percentile

As shown in Figure III.A 18, at the 99.9th percentile, the total cumulative risk (all pathways) was as low as 91 for this age group and nearly all of the estimated exposure came through the oral route that included significant contributions from drinking water and food pathways. Water exposure along with food exposure caused a slight excursion below an MOE of 100 for a short period of less than a month. Food contributed a consistent MOE average of 280. Dermal MOEs are above 1,000. Inhalation MOEs were greater than ca. 140.

d. 21-day rolling average, adults 50+ years, Region A, no oxon Florida

The results of the total cumulative assessment for adults 50+ years using the BMD_{10} of the index chemical (methamidophos) for the PoD are presented in Appendix III.A Temporal Exposure Profile Plot for Florida Water Figure III.A 19, Figure III.A 20, and Figure III.A 21

95th Percentile

As shown in Figure III.A 19, the consistent significant source of pesticide risk from exposure to pesticides at this percentile of exposure is through the food pathway with total MOEs as low as 420 with an average MOE of 890. Food MOEs stayed near 810.

Inhalation and dermal exposures that are associated with residential use are typically rather low at this percentile with MOEs greater than 20,000 and 6,700, respectively. Drinking water shows a spike for a period of less than 30 days where the lowest MOE reached was ca 580 and averaged around an MOE of 18000.

99th Percentile

As shown in Figure III.A 20, the daily total MOEs ranged from 230 to 500. At this percentile, the daily MOE values from drinking water sources ranged from 280 to ca. 99,000 and comprise the major source for total exposure with the lowest MOEs occurring for about three weeks beginning mid-August. Food exposures have consistent MOEs averaging 510. MOEs associated with the dermal route are generally greater than 14,000. Inhalation exposure resulted in average MOEs of 1,400.

99.9th Percentile

As shown in Figure III.A 21, at the 99.9th percentile, the total cumulative risk (all pathways) was as low as 130 for this age group and nearly all of the estimated exposure came through the oral route that included significant contributions from drinking water and food pathways. Drinking water exposure results in water MOEs as low as 150 with an average of 17000. Food contributed a consistent MOE, average MOEs were just above 240 at 240. Dermal MOEs are above 1100. Inhalation MOEs were greater than ca. 600.

G. Risk Characterization

1. Introduction

Risk characterization is the interpretation phase of the assessment process. The present chapter characterizes the risks identified as part of this Organophosphorus Cumulative Risk Assessment (OP CRA) update. The intent is to note and discuss uncertainties and strengths in the hazard and exposure elements of risk estimates and to assess quantitatively (when possible) or qualitatively the potential impact of those uncertainties on the risk estimates.

Proper and appropriate risk characterization is particularly important for an assessment as complex as the OP CRA. Many types of data derived from a variety of sources have been combined to produce estimates of risk from exposure to multiple OPs in food, drinking water, or from residential use. The outputs of the assessment should be evaluated in a variety of ways. Potential biases in input parameters, the direction of the bias, and the uncertainty surrounding the inputs and the exposure model must be considered with regard to their potential impact on the results of the assessment. Sensitivity analyses are important as is a description of how changes in input assumptions might – or might not— affect the assessment.

OPP has reflected in this updated OP CRA completed risk mitigation measures from the single chemical assessments. The current document presents the estimates of risk associated with exposures to OPs in food, drinking water and from residential uses as a set of temporal or time-series plots of MOEs over a period of 365 days. Contributions from various pathways and routes of exposure are arrayed separately. The results are presented graphically for the regions for the 1-2 year old, 3-5 year old, 20-49 year old, and 50+ year old age groups No single value in the assessment should be used to independently arrive at the interpretation of the results. As discussed below, interpretation of the assessment depends upon the synthesis of a vast body of information about the input data and the processing of that data to determine whether estimated risk is below OPP's level of concern.

2. Hazard and Dose-Response Assessment

The hazard and dose-response assessment is presented in detail in section I.B of the 2002 Revised OP CRA. That section outlines the steps in developing the dose-response relationships for each pesticide and its capacity to inhibit acetylcholinesterase in the brain of female rats. It includes a description of all of the data used in the dose-response

analyses. Reasons for the selection of methamidophos as the index chemical for the OP cumulative risk assessment are also discussed. In addition, Section I.B of the 2002 Revised OP CRA describes the exponential dose-response model used to develop the dose response curves that provided the basis for developing the RPF for each chemical and the PoDs for the index chemical for each route of exposure (i.e., oral, dermal, and inhalation).

The major conclusions from the 2002 revised CRA regarding the RPFs, PoDs, and selection of methamidophos as the index chemical are summarized in this update. A discussion of the intra-species, and inter-species factors and the FQPA 10X factor for the protection of infants and children are also provided in this update.

a. Acetylcholinesterase Inhibition: Data Quality & Common Effect

The first step in deciding that a cumulative risk assessment was needed was the determination that the OPs were toxic by a common mechanism, i.e., cholinesterase inhibition via phosphorylation of the active site of the enzyme. This determination was subjected to peer review by the Scientific Advisory Panel in 1998. Once a common mechanism was identified, the next step in the process was to select an appropriate method for combining the risks from exposures to several pesticides from more than one source/route. A large body of data describing the inhibition of acetylcholinesterase in plasma, RBCs, and brain has been generated for each registered OP. OPP has elected to use the brain acetylcholinesterase data from female rats as the basis for developing RPFs and PoDs for use in the assessment. Brain acetylcholinesterase inhibition was selected as it reflects a response in a target tissue of concern that is relevant to humans. Although RBC and plasma cholinesterase inhibition do reflect exposure to OPs and, therefore, the potential for adverse effects, brain acetylcholinesterase inhibition is an indication of direct effects upon the target tissue itself. Error due to the extrapolation between the response in a surrogate tissue (i.e., red blood cell and plasma) and a target tissue itself (brain) is eliminated. In addition, the data for the brain compartment have very narrow confidence limits when compared to those from the plasma and RBC compartments, suggesting that there is much less variability in this compartment across the data base. OPP is confident that the assessment as performed is scientifically and statistically sound and based upon a reliable data set

b. Dose-Response Analysis

This assessment uses the RPF approach. Briefly, the RPF approach uses an index chemical as the point of reference for standardizing the common toxicity of the chemical members of the cumulative assessment group. RPFs (i.e., the ratio of the toxic potency of a given chemical to that of the index chemical) are then used to convert exposures of all chemicals in the cumulative assessment group into exposure equivalents of the index chemical. The RPF approach utilizes dose-response information to provide an estimate of each OP's potency for the common toxicity, and thus allows for the quantification of exposure as it relates to the joint risk of the cumulative assessment group. OPP selected the RPF approach based upon the relatively rich oral toxicity data base on cholinesterase inhibition available for the OPs. Although a biological or pharmacokinetic modeling approach would have advantages in determining the cumulative risk for these OPs, the input parameters for such an approach are not available. Thus, the pharmacokinetic (PK) characteristics of the OPs could not be incorporated in the dose-response assessment which would allow for a more refined estimate of the combined risk to humans. Therefore, OPP has applied simple dose addition and has used an empirical curve fitting model to determine RPFs and PoDs.

OPP, in collaboration with ORD, developed an exponential model to describe the oral dose response curves for each OP that permitted fitting of a combination of cholinesterase activity data from different studies to derive a BMD. This model has been previously subjected to extensive public comment and peer review by the SAP (FIFRA SAP 2001b, 2002a). Although a PK model might be considered an ideal approach, the SAP regarded the exponential model to be appropriate for derivation of RPFs and PoDs for the data being analyzed. The statistical model used, to the extent supported by the data, a flat region (or “shoulder”) at the low dose portion of the dose response curve to reflect more appropriately cholinesterase inhibition at very low doses. OPP believes that the model fitting procedure used in this assessment provides reliable estimates of relative potency for the oral route and PoDs for all routes The cholinesterase data used for the oral route of exposure were quite extensive and, in general, of good quality for dose-response modeling. The data for the inhalation and dermal routes tended to be less extensive and not as robust for dose response modeling for most of the OPs with residential uses

A BMD_{10} was selected as the basis for comparison of the dose-response curves for the OPs. OPP's goals in selecting a point of comparison were to choose a point in the observed response range,

but low enough on the curve to reduce the impact of any lack of proportionality between response that might result from deviation from the assumption of proportionate dose response between OPs. In addition, OPP was concerned that the magnitude of the response (cholinesterase inhibition) be sufficient to ensure that it was reliably distinguishable from background and stil be protective of behavioral and functional effects. A power analysis of the data used in deriving the 21-day steady state determination indicated that there was insufficient power to distinguish the change in cholinesterase inhibition reliably below 10% inhibition.

c. Selecting the Index Chemical

OPP selected methamidophos as the index chemical for the OP CRA. Methamidophos has sufficient data for cholinesterase inhibition to support modeling of a BMD_{10} by all three routes of exposure. The high quality dose response data for methamidophos permits reliable estimates of PoDs for all routes without resorting to the use of the less precise NOAELs. Certainty in the PoDs was considered to be of great importance in as much as they will impact the overall uncertainty in the entire risk assessment. OPP has elected to use the central estimate of the BMD_{10} instead of the $BMDL_{10}$. This decision reflects the complexity brought to the analysis by the joint consideration of multiple studies for multiple chemicals and the high quality of the methamidaphos toxicity database. For methamidophos, the BMD_{10}s and the $BMDL_{10}$s were very similar suggesting good dose response data with little variability and a very good fit of the data to the model.

d. Assumption of Dose-Additivity

The cumulative risk assessment for the OPs is based on the assumption of dose additivity. Dose additivity is the Agency's assumption when evaluating the joint risk of chemicals that are toxicologically similar and act at the same target site (USEPA 2001a). The SAP (FIFRA SAP, 2001a) indicated that substantial reliance would have to be placed on what is known about the mechanism of toxicity because it is very difficult to prove dose additivity at human exposure levels. They further pointed out that studies available on individual chemicals were usually not designed to address the issue of dose additivity.

The mathematical definition of dose addition requires a constant proportionality among the effectiveness of the chemicals (USEPA 2001a; Hertzberg et al., 1999). Thus, an important objective in the dose response assessment is to evaluate whether dose-response relationships are consistent with the assumption of dose additivity.

There is some uncertainty surrounding the assumption. Two different versions of the exponential model have been used in this assessment. Approximately half of the pesticides were fit using a model with a flat low dose region while the remaining OPs were fit using a model which is linear in the low dose region. In addition, the OPs did not exhibit common horizontal asymptotes (P_B); rather the P_Bs vary among chemicals. Both of these factors indicate that the dose-response curves are not parallel.

Dose additivity assumes that the common mechanism chemicals behave in a similar fashion (i.e., same pharmacokinetics and pharmacodynamics). In reality, these common mechanism chemicals may not exhibit the exact same pharmacokinetics and pharmacodynamics. Biotransformation of OPs is extremely complex and involves several metabolic systems in different organs (e.g., reactions involving cytochrome P450 isoenzymes, hydrolysis by esterases, and transferase reactions; see Nigg and Knaak, 2000). The differential activation and/or deactivation of OP pesticides has not been well documented in the literature, nor have the human metabolic pathways (Mileson et al., 1998). At this time, these pesticides cannot be separated into subgroups based on pharmacokinetic or pharmacodynamic characteristics. Thus, current information on OP metabolism does not provide a sufficient basis to depart from dose additivity at low levels of exposure anticipated to be encountered environmentally.

The application of dose additivity requires the assumption of no interactions other than additive among the chemicals at low doses. There are a limited number of investigations of the toxicity of combinations of organophosphorus substances, not necessarily pesticides, that are known to inhibit cholinesterase enzymes (For example see Dubois, 1961 and 1969; Frawley et al., 1957 and 1963; Calabrese, 1991; Cohen, 1984; Eto, 1974; Su et al., 1971; Casida et al., 1963; Keplinger and Deichman, 1967; Rosenberg and Coon, 1958; El-Sebee, et al., 1978; Seume and O'Brien, 1960; Singh, 1986; Mahajna et al., 1997; Serat and Bailey, 1974; Richardson, et al., 2001; Karanth et al., 2001; Karanth et al, 2004; Abu-Qare , et al., 2001a; Abu-Qare et al., 2001b). Most of the studies reviewed were high dose studies that investigated the acute lethality (LD_{50}) of combinations, mostly binary, and not the cumulative effects of low exposure levels from multiple OPs. A number of these studies were conducted using intraperitoneal (i.p.) administration which confounds interpretations of effects that may be expected by the oral, dermal, or inhalation routes. One recent study used a binary mixture of chlorpyrifos and parathion in neonatal rats (Kacham et al, 2006). Timchalk et al (2005) showed that at low doses that there were no pharmacokinetic and

pharmacodynamic interactions following exposure of chlorpyrifos and diazinon to adult rats.

The most robust mixture studies with OPs come from Moser et al. (2005 and 2006) who evaluated the toxicity of a five OP mixture to adult and pre-weanling rats. Experimental dose levels were based the relative proportions of each OP found in the US diet based on estimates from EPA risk assessments. The study design included doses ranging from approximately 20% or less ChE inhibition up to 80% ChE inhibition. Using a ray design, Moser et al. (2005 and 2006) showed little deviations from the assumption of dose additivity. In the adult and preweanling studies, the ED_{20} and ED_{50} for brain and blood ChE were only up to 2-fold lower than that predicted by dose additivity.

Overall, the studies reported in the literature do not provide a basis for concluding that interactions between OPs will result in significant departure from dose addition at low doses. Nevertheless, this literature provides data showing that different types of interactions can occur between OPs and that the magnitude of the interaction appears to depend on the specific combination of OPs investigated, the dose-levels administered, and also the sequence of exposure (Singh, 1986; Pope and Padilla, 1990, Karanth et al., 2001, Karanth et al., 2004, Kacham et al., 2006). In particular, the data available are not sufficient to establish the nature of interactive effects on cholinesterase activity that may be expected among OPs at low exposure levels.

The OPs all act on the same target site– namely, the inhibition of acetylcholinesterase by phosphorylation in nerve tissue, which elicits a variety of cholinergic effects. Dose addition is regarded as a reasonable and appropriate approach for estimating the cumulative risk associated with joint exposure to the OP common mechanism group. At this time, there is not sufficient basis to depart from dose additivity.

2. Food Assessment

The food component of the OP cumulative risk assessment is based primarily upon two extensive, reliable data sets: 1) USDA's Continuing Survey of Food Intakes by Individuals, 1994-1996 and 1998 (CSFII) and 2) USDA's Pesticide Data Program. The CSFII provides a detailed representation of the food consumption patterns of the US public across all age groups, during all times of the year, and across the U.S. The PDP data provide a very reliable estimate of pesticide residues in the major children's foods. They also provide an indication of the co-occurrence of OPs in the same sample, alleviating much of the uncertainty about co-occurrence in foods that are monitored in the program. These

two data components provide a firm foundation upon which to assemble other data to develop the OP cumulative risk assessment and are discussed in more detail below.

a. Consumption Data

As with the previous OP CRAs, this updated OP assessment is based on dietary consumption data obtained from the USDA's CSFII in years 1994-96/1998. This is an extensive two-part (1994-1996, and then 1998) survey and includes more than 20,000 individuals sampled over four years. The CSFII 1998 provided an additional 5,559 consumption diaries for children ages newborn through nine years of age, which supplemented the 4,253 children sampled in the CSFII 1994-96. This additional, supplemental children's survey was specifically requested of USDA by OPP in order to improve our ability to assess exposures to children. In each year of the survey, approximately 5,500 participants in 62 geographical areas across the country were interviewed on their dietary consumption over two separate (non-consecutive) days. The survey was designed to provide a nationally representative sample of non-institutionalized persons residing in the US. USDA also provides sampling weights, which allow the survey results to be projected to the US population.

The sampling procedure was designed to account for variability in individual consumption patterns (e.g. types and amounts of foods eaten) due to differences in age, gender, ethnicity, regional location, and socioeconomic status. Also survey respondents are interviewed on different days of the week throughout the year to account for seasonal and within week variability in consumption patterns. A number of other aspects of the survey are also controlled in order to maximize the prospect that the results are representative not only of the entire U.S. population, but also particular subgroups, including those for which OPP generates acute dietary food exposure distributions.

While the USDA food consumption surveys are designed to be generally representative of the U.S. population, it is clear that some factors that can influence dietary choices are not addressed in the survey design. For example, the CSFII surveys do not purport to be representative of people in institutional living arrangements (colleges, nursing homes, etc.) or of different religions or health status. Specific subpopulations such as vegetarians, those on restricted diets, or those on specialized diets were not specifically surveyed. In addition, smaller specialized subpopulations such as Native Americans or subsistence fishermen are not specifically targeted. Overall, however, the dietary information which OPP used as part of this preliminary

cumulative assessment for the OP pesticides is extensive, of high quality, and fully representative of many of the subgroups in the U.S. population. OPP is confident that the consumption data available from the CSFII 1994-96/1998 provide a reasonable basis for estimating exposure for the subpopulations surveyed to OPs in foods.

b. PDP Monitoring Data in the Assessment

USDA PDP data are used for most of the pesticide residues in food assessment. PDP samples fruits, vegetables, juices, meats, and dairy products at central distribution centers and warehouses immediately prior to distribution to supermarkets or grocery stores. The samples are washed and inedible portions (e.g., cores, peels, etc.) removed prior to analysis. PDP data, thus, closely reflect residues in foods, as consumed. To account for various cooking and processing factors that might reduce residues further (e.g, cooked potatoes, canned beans). OPP has applied these factors, where available, to the PDP data. Thus, pesticide residue data from PDP accurately represent pesticide concentrations to which consumers are exposed.

In addition the use of PDP as a source of residue data has a number of inherent benefits that preclude the need for the use of conservative assumptions in the assessment. The PDP sampling design and procedures provide OPP with a nationally representative sample of selected food commodities available to the US population in grocery stores. OPP assumes a uniform distribution of these food commodities across the US. The assumption of nationally uniform distribution of foods does not reflect highly localized consumption events that may be encountered by individuals who obtain foods at road side stands and consume it closer to the time of harvest than the foods available in larger grocery stores. However we anticipate that only a small percentage of food consumed would be affected.

PDP provides a direct measure of the occurrence of more than one OP in any sample analyzed. OPP can use these data as an indication of pesticide co-occurrence likely to be encountered in foods, and extrapolate accordingly. In addition to providing a nationally representative sample, the PDP data provides OPP critical information regarding the co-occurrence of pesticide residues in those foods. PDP data also appropriately reflects existing use and usage practices inherent in the data. Given the size, scope, and breadth of the PDP data, little uncertainty is introduced by the use of these data.

PDP tests for many oxon metabolites of the OPs included in the dietary assessment. The majority of these oxons have not been found in detectable amounts in the food commodities sampled. Omethoate,

the dimethoate oxon, is the only OP oxon found in a significant portion of PDP commodities. All other OP oxons contribute an insignificant amount to the overall food exposure.

In contrast to single chemical assessments, where non-detectable residues in food commodities are assumed to be present at one-half the limit of detection (LOD) of the analytical method, PDP samples with non-detectable residues are assumed to be "zero" values in this assessment. Although the result of replacing all non-detectable residues with "zero" values would intuitively suggest an under-estimation bias, OPP has demonstrated through its case study that this change has little impact on the upper end of the exposure distribution for the OP's, upon which regulatory decisions are based. This result is not surprising given the number of chemicals involved in the OP CRA. The impact of this assumption was tested in the original OP Cumulative Risk Case Study (USEPA, 2000c) that was presented to the SAP in December 2000. In this original OP Case Study, a similar use of PDP data as the residue data source in this assessment was demonstrated for 24 OPs. The resulting data set had characteristics very similar to the one used in the current assessment, and the analysis performed at that time demonstrated that the use of the "zero" values had only negligible impact on the MOEs of the upper percentiles of exposure. This is not unexpected: generally, the LODs for PDP data are very low (the average LOD for the entire data base is about 0.01 ppm) and the vast majority of exposures at the upper percentiles are derived from detectable residues in a single commodity rather than multitude of ½LOD values. Therefore, it seems reasonable that the effect of assumptions related to estimation of values below the LOD would not significantly influence exposures at the highest percentiles of exposure.

c. Data Translation from PDP

Not all foods to which OPs are applied are monitored in PDP. OPP has developed a procedure by which commodities that are measured by PDP serve as surrogate data sources for commodities that are not. This approach is outlined in OPP/HED SOP 99.3 (USEPA, 1999b). It is based upon the concept that families of commodities with similar cultural practices and insect pests are likely to have similar pesticide use patterns. Although this approach is generally sound, it introduces uncertainty with regard to how similar the use patterns for a given pesticide are to those for even closely related commodities.

For example, the same OP may be applied to several crops belonging to the same crop group (or family) on a similar time schedule. However, the application rates and/or the number of

treatments may differ between the treated crops. Such issues should be taken into consideration when conducting sensitivity analyses of the results of the risk assessment. When the data are adapted for the use of several chemicals simultaneously, and estimates of co-occurrence are derived from that data, the likelihood of an inappropriately assigned residue becomes greater. Although the commodities may have similar cultural practices, the translation from one commodity to another implicitly assigns the inherent percent crop treated information from one commodity to another. The direction and magnitude of this error will differ from one commodity to another. However, the magnitude of the error is probably not great in that the commodities for which PDP data were translated represent only ~1% of a child's diet and none of these crops were significant contributors to exposure.

d. Other Sources of Residue Data

The PDP program provides pesticide residue data for a variety of fruits, vegetables, grains, beef, dairy products, and chicken. Nevertheless, PDP data and surrogate PDP data do not cover all commodities of interest. For example, PDP does not include data for seafood and eggs; for these commodities, FDA's Total Diet Study and FDA Monitoring data were reviewed. The analytical results from these data sources are based on low LODs and suggest that eggs and seafood contain negligible residues of OPs. OPP thus used a zero to represent concentrations in these commodities. OPP considers this factor neutral with regard to the impact on the results of the assessment.

Approximately 3% of the foods consumed by children 1-2 years of age still remained unaccounted for after considering the FDA Total Diet Study and FDA Monitoring data. Sugar, molasses and syrups were assigned a residue value of zero. These products are highly processed commodities that are unlikely to retain any significant residues following the intensive processing procedures they undergo. The limited data from the Total Diet Study found no residues in pancake syrup or sugar. Likewise, no data are available for field corn or dried beans. These commodities are also blended and highly processed before consumption. OPP believes that omission of these foods from the assessment will not result in a significant under-estimation of exposure to OP pesticides from food for children.

e. Impact of Regulatory Actions

There has been a significant reduction in OP use sites and use patterns as a result of the individual chemical decisions. In cases for

which legal agreements have been signed or voluntary cancellations implemented, the uses have been removed from the assessment. Examples include food uses of methyl parathion and dimethoate (see Chapter 1 for additional details regarding the specific cancellation actions that have taken place). For other pesticides, pre-harvest intervals have been extended or rates have already been reduced. To the extent that they are not yet apparent in the monitoring data available, these changes are not reflected in the assessment. This assessment has incorporated domestic use cancellation information that was announced recently by the Agency concerning the phase out of the remaining (Group 3) uses of azinphos-methyl (AZM). Specifically, all domestic uses for AZM on almonds, Brussels sprouts, pistachios, walnuts, apples, blueberries, cherries, parsley, and pears are to be phased out effective in 2007 or 2010. This information was incorporated by removing from the assessment all AZM residues on these crops which are domestically-grown; residues on imported crops were not changed[21]. All other uses of this pesticide have already been voluntarily cancelled by the manufacturer.

Finally, to evaluate the degree to which use practice changes over time may or may not have affected the estimated exposures and risks, OPP performed a sensitivity analysis in which only the most recent PDP data (2000-2004) was used. Specifically, OPP ran a second, supplemental analysis which used only the last five years of PDP data (except for a few commodities like frozen green beans, grape juice, and fresh peas that were not sampled from 2000 to 2004). The purpose of this analysis was to determine if the elimination of earlier (pre-2000) PDP data which might be considered less typical of current use patterns and practices would significantly affect the exposure and risk estimates. Under this scenario, the MOEs for children 1-2 and 3-5 years old increase from 108 to 111 and from 99 to 103, respectively. The use of only the most recent PDP data might be considered to be more reflective of current exposure levels and this analysis indicates that the use of the complete PDP data set may over estimate to some degree the extent of current risk.

[21] These mitigation actions were proposed due primarily to issues associated with worker, and ecological risk not dietary exposure and risk. Thus, dietary risk and exposure estimates presented in this document are not expected to differ significantly from those that that do not incorporate these 2007 and 2010 AZM proposed use cancellations. As a sensitivity analysis and to ensure that risks prior to any use cancellations are not above the Agency's level of concern, OPP has also performed a parallel exposure analyses in which domestic uses *are retained*. Resulting exposure and risk estimates under this scenario would be expected to be more typical of the near term (e.g., through 2007 and 2010). When these AZM uses are included in this alternative assessment (i.e, incorporated back into the exposure and risk calculations), MOEs change from 108 to 107 for Children 1-2 and from 99 to 98 for Children 3-5. Thus, the AZM use cancellations that have been proposed are not expected to have any significant impact on the dietary risk estimates for the most exposed subpopulations. This supplemental assessment is described in additional detail in Appendix II.G.1.

f. Model Outputs

The food component of the OP cumulative risk assessment was conducted using the DEEM Calendex software. This program evaluates the full range of dietary exposures. It permits a detailed evaluation of the source of exposures with regard to which foods and pesticides are the likely sources of the exposure. This analysis served as the basis for determining which commodity/pesticide combinations warrant further scrutiny in the event that further regulatory action is determined to be needed.

The results of the food portion of the revised OP cumulative risk assessment are summarized in Table I.G-1 (the detailed discussion is presented in Section I.C of this document). The results are presented in the form of MOEs for children 1-2 years of age and 3-5 years of age and for adults 20-49 years and 50+ years of age. This was done for the 95th, 99th, 99.5th, and 99.9th percentiles of exposure for each age group. The 1-2 year old and 3-5 year old age groups are consistently the most highly exposed subgroups in the analysis. MOEs from both the single day and 21-day are presented although, (as described in section B of this document and in appendix II.B.4) the 21- day risk estimates are more appropriate.MOEs from the 21-day analyses. These estimates either exceed or are very close to the target MOE of 100 (Table I.G-1). The MOEs at the 99.9th percentiles of exposure for children 1-2 and children 3-5 years old are 107 and 99 respectively. MOEs for the single-day assessment do not reach the target value of 100 at the 99.9th percentile (Table I.G-1). The MOEs at the 99.9th percentile of exposure for children 1-2 and children 3-5 years old are 31 and 35 respectively. MOEs of 100 were reached at approximately the 99.3rd and 99.5th percentile of exposure for children 3-5 years old and children 1-2, respectively.

OPP has evaluated the consumption records occurring in the tail of the distribution to ensure that they reflect reasonable consumption patterns. Analysis of the tail of the distribution (>99th percentile) indicates that no small subset of consumption records dominates the outcome. This observation increases OPP's confidence that the food and water components of the assessment are not unduly influenced by unusual consumption patterns and reflect the consumption habits of the public at large.

Table I.G-1 Summary of OP Cumulative Food Assessment.

Children 1-2 Route: Food*	Percentile	Exposure Period Single Day Analysis MOE**	Exposure Period 21-day Analysis MOE**
	95	440	550
	99	130	250
	99.5	79	190

*The additional FQPA Safety Factor is included as an adjustment to the chemical-specific Relative Potency Factors
**MOEs were calculated using Calendex software and thus represent a mean MOE

Children 3-5 Route: Food*	Percentile	Exposure Period Single Day Analysis MOE**	Exposure Period 21-day Analysis MOE**
	95	520	670
	99	160	300
	99.5	98	220
	99.9	35	99

*The additional FQPA Safety Factor is included as an adjustment to the chemical-specific Relative Potency Factors
**MOEs were calculated using Calendex software and thus represent a mean MOE

Adults 20-49 Route: Food*	Percentile	Exposure Period Single Day Analysis MOE**	Exposure Period 21-day Analysis MOE**
	95	800	820
	99	290	610
	99.5	180	470
	99.9	76	280

*The additional FQPA Safety Factor is included as an adjustment to the chemical-specific Relative Potency Factors
**MOEs were calculated using Calendex software and thus represent a mean MOE

Adults 50+ Route: Food*	Percentile	Exposure Period Single Day Analysis MOE**	Exposure Period 21-day Analysis MOE**
	95	800	810
	99	240	510
	99.5	150	400
	99.9	65	240

*The additional FQPA Safety Factor is included as an adjustment to the chemical-specific Relative Potency Factors
**MOEs were calculated using Calendex software and thus represent a mean MOE

3. Residential Assessment

The residential component of the OP cumulative risk assessment incorporates probabilistic input distributions and factors in seasonal and regional aspects of pesticide use by using a calendar-based approach. The use of a calendar-based model is necessary in order to appropriately incorporate and account for the timing of pesticide applications and for delineating subsequent exposures in the general population. These models employ distributions of the available residue and contact exposure data and are able to capture the inherent variability in the exposed population and can be used to provide justification regarding co-occurrence of pesticide exposure events. This method is preferable to relying solely on point (or default) estimates and combining "what if" scenarios; such practices only compound conservatism or add uncertainty while providing little information to risk managers regarding the potential numbers of exposed individuals and the potential range of exposures. The Calendex model used here provides the ability to evaluate route specific pathways which are defined by the model user so that more appropriate input values (e.g, residue and residue contact data) can be more fully used.

Three types of data are used in the residential assessment: pesticide use; pesticide residue dissipation; and exposure contact and exposure factors. Pesticide use data are used to determine the percent of households using a pesticide, the timing of the pesticide treatments, frequency and duration of exposure. Pesticide residue dissipation data address the fate of the pesticides once applied to an environment (e.g., lawns). Exposure contact data are scenario-specific metrics that relate human exposure to pesticide residues. Humans come in contact with the residues by contacting the product directly or by contacting the residues left after the pesticide applications are made. Distributions of human exposure factors, such as breathing rates, body weight and surface areas used in this assessment come from the Agency's Exposure Factors Handbook. These will not be discussed in the risk characterization of the document because the values are established and used throughout the Agency.

The residential scenarios addressed in this 2006 Update represent OP uses that have the potential for significant exposure or risk when considered in a cumulative assessment. The uses considered in this assessment include golf course and lawn care applications, home gardens, public health sprays, indoor uses (including impregnated pest strips and aerosol spray can), and pet treatments (including pet, collar, aerosol, liquid, and powder uses).

Since the release of the 2002 document, OPP has mitigated a number of uses with respect to several OPs. All uses of fenthion and fenamiphos have been cancelled and therefore have not been included in the 2006 Update. A number of DDVP uses also have been cancelled or otherwise mitigated. Specifically, cancellation has been requested for the total release fogger, crack and crevice uses, the 21 g and 100 g pest strips, and lawn products and these uses are therefore are not included in this assessment. The indoor uses that remain for DDVP and are included here-- are the 5 g- , 10 g- , and the 16 g-strips; the pet collar; and the indoor aerosol spray. While large (65g and 80g) uses will remain, the labels will be modified to include language restricting use to only unoccupied areas and dwellings that remain unoccupied for more than 4 months. Therefore, since restricted use of the large strips is not expected to result in significant exposure, the indoor use of large DDVP pest strips was not assessed in the report. The DDVP registrant has requested registration of a new 16 gram pest strip. For this reason, this 2006 Update includes consideration of the 16 gram pest strip use.

Additionally, an assessment of exposure from tetrachlorvinphos pet collars was not explicitly included in this assessment. While the tetrachlorvinphos pet collars have not been assessed, the CRA does address the use of tetrachlorvinphos pet shampoos, sponge-on treatments, and powders. Exposure from the shampoo, sponge-on and powder treatments is likely to be higher than from pet collar use. This is because greater amounts of active ingredient are applied and larger areas of the pet are being treated. Although tetrachlorvinphos treated pet collars represent the largest usage of the product, the number of people treating pets with the liquid and powder products were adjusted upwards to reflect the collar use in addition to the use of the other products. **Thus, pet collar uses were implicitly considered or accounted for by assuming exposures from this use are similar to that of shampoo, sponge-on, and powder treatments.** The usage data was taken from National Home and Garden Pesticide Use Survey (NHGPUS).

Each data set used in the assessment introduces some potential bias in the outcome of the exposure assessment. A summary of these biases, their direction and magnitude, is presented in Table I.G-2.

a. Pesticide Use Data

Pesticide use data include regional site/pest markets, timing of application, and the percent of households using their products. In the absence of specific pesticide use information, OPP developed exposure scenarios based on timing aspects found in regional Cooperative Extension Service publications and surveys such as the NHGPUS, the National Garden Survey, and Doane's GolfTrak. The

Cooperative Extension Service publications were useful for establishing the timing of various turf chemicals. The survey data were used to establish the number of households that may use a given pesticide. The NHGPUS delineates percent of households using pesticides based on a large national survey. These values consider users and nonusers as well as homes having lawns and those that do not. The use of this survey introduces uncertainty into the analysis because of the age of the survey (1989-90). The data may not reflect reductions in current OP use patterns and therefore overestimate exposure. Doane's GolfTrak was used to identify the percent of golf courses treated with pesticides and is timelier (1998-99). OPP believes this is a robust data source. The National Garden Survey has been tracking percent of households employing lawn care applicators and is considered very robust. In addition, variables such as vegetable garden size are well characterized since these gardens are easy for survey respondents to define.

b. Exposure Contact and Pesticide Residue Dissipation Data

i. Dermal Exposure

Dermal exposure to pesticides may occur during application and post-application activities. Examples of application activities that might result in pesticide exposure include, but are not limited to, spraying liquid pesticide formulations on ornamental plants, or applying granular formulations to residential turfgrass.

The application of pesticides is one of the more straight-forward activity patterns to measure since it represents easily defined activities. As a result, exposure contact data used to assess exposures experienced by the applicator of consumer oriented pesticides is by far the most robust information used in the residential portion of this assessment. Data generated by the Outdoor Residential Exposure Task Force (ORETF) have been used to assess the use of hose end sprayers (lawn care products), rotary granular spreaders (lawn care products), hand pump sprayers (home gardens and orchards) and hand held dusters (home vegetable gardens). Another study, submitted by a registrant, was also used to assess residential applicator exposure using granular shaker cans to apply disulfoton. Exposure contact data used to address the pet scenarios include chemical specific exposure data. All studies meet or exceed current Agency guideline requirements. OPP has high confidence in the use of these data.

There are three post-application dermal exposure scenarios addressed in this assessment. These are: post-application exposure to vegetable and home garden pesticide applications, post application dermal exposure to lawn care products, and post-application dermal exposure to pet care products.

Like the applicator scenarios, the post-application garden exposure scenarios are easily defined activities. For harvesting vegetables or weeding, there is a substantial amount of data based on farm worker exposure performing similar activities in crops requiring substantial hand labor. These contact values have the potential to overestimate exposure since they are based on individuals working for profit based largely on their productivity. Such workers are likely to be more efficient and therefore exposed to a larger amount of treated surface than most home gardeners. A uniform distribution of values representing hoeing and harvesting may overestimate early season activities that consist of potential exposure to small plants.

Dermal exposure from post-application contact with the lawn chemicals is equally varied. Contact data, representative of the range of human activities has been difficult to model. Dermal contact exposure values were identified in data described in Vaccaro et al. (1996), for adults who performed scripted activities and contact values for children performing non scripted activities on lawns treated with a non-toxic substance were described by Black (1993). Rates of pesticide transfer in the studies with surrogate compounds were similar to those observed in the chemical specific dissipation data available to OPP.

Turf transferable residue data are available for all turf chemicals. The residue dissipation data used in this assessment were conducted at a variety of locations representative of the climatic conditions across the United States. These data are of good quality and provide accurate estimates for this parameter.

There are no chemical specific data that measure the influence of wet hands and the mouthing behavior of young children on the efficiency of residue transfer. OPP considered a study performed by Clothier et al. (2000) in which he observed an increase in transfer efficiency (1.5- to 3-fold) when comparing a turf residue collection method to volunteers pressing dry hands or hands wetted with saliva. He observed a higher transfer rate for the compound with the lowest application rate. This may suggest that the hand surface becomes saturated and thus results in a lower transfer rate at higher application rates. The factor of 1.5- to

3-fold was used in the assessment. The factor may overestimate the transfer of residues at higher application rates.

Tetrachlorvinphos specific data addressing exposure of individuals while treating pets and post-application pet fur measurements were used in this assessment. To assess post application dermal exposure, an exposure study of 16 pet groomers, each exposed to 8 dogs treated with carbaryl, was used. Dermal transfer coefficients were generated based on the transfer efficiencies of the tetrachlorvinphos pet fur data and the measured exposure of the groomers. Duration of exposure was based on video analysis of children (n=3) playing with pets (Freeman et al., 2001). At this time the method OPP is using in this assessment is the best available as it uses chemical specific data (applicator and fur residue), and real world contact data (groomers and video analysis of children).

ii. Incidental Oral Exposure

Incidental oral ingestion is an important exposure pathway in the residential assessment. Frequencies of hand to mouth events used in the assessment are based on real world observations of children in homes and day care centers enumerated on video tape. However, a number of issues surround the estimation of the impact of this activity. The number of hand-to-mouth events occurring in a given time frame was developed by observing children's behavior during quiet play. Video tape data are based on children situated indoors and not outdoors. Hand to mouth frequency may be higher when children are engaged in "quiet play" (e.g., listening to stories) than when engaged in active play (running, tag, etc.). Children playing on lawns are likely to be engaged in active play. Therefore, the frequency of hand-to-mouth events used in the current assessment may be an overestimate.

The variety of hand-to-mouth events (such as the hand being near the mouth rather than in it) makes the enumeration of events difficult. Further, video tape values provide no information on rate of transfer from treated surfaces to hands. Transfer estimates in the assessment were based on studies measuring wet hand transfer efficiency with wet hands using surrogate compounds. No chemical specific data are available. Also, implicit in all hand to mouth exposure estimates, is the constant replenishment of residues on the hands between each mouthing event. However, it is unlikely that replenishment occurs between each contact. For instance, if a child contacts an untreated surface after touching a treated surface, a portion of the initial residue will

be transferred to the untreated surface and therefore not available for transfer to the mouth during a subsequent mouthing event. Assuming constant replenishment of residues between mouthing events is expected to overestimate incidental oral exposure.

iii. Inhalation Exposure

Post-application inhalation exposure accounts for a large portion of the overall residential exposure. To estimate post-application inhalation exposure, OPP obtained information on time-activity data from the US EPA ORD Consolidated Human Activity Database (CHAD) (http://www.epa.gov/chadnet1/). For each specific age group, OPP used information from CHAD diaries to link an individual's breathing rate with a specific activity. This was done to account for the interrelationship that exists between the activities that an individual engages in and the breathing rate with which that activity is connected. This assessment is based on more sophisticated methods than is typically used to assess post-application inhalation exposure and relies on the best available data. For these reasons, OPP has high confidence in the resulting exposure estimates.

c. Oxons

Some residential-use OP pesticides are themselves oxons (such as acephate, naled, DDVP, and tetrachlorvinphos) or convert to oxons (e.g., trichlorfon to DDVP). These OP pesticides were considered in the residential assessment using chemical-specific residue data. Additionally, some other OP pesticides degrade to form oxons that themselves are not registered active ingredients. Specifically, these include disulfoton, bensulide, and malathion. Since there are no available residue dissipation or decay data to quantify the amount of oxon formation resulting from residential uses of bensulide, disulfoton, or malathion, a sensitivity analysis was conducted to determine the relative oxon contribution to overall cumulative risk. OPP performed this sensitivity analysis by increasing bensulide and disulfoton residues by a factor of 10 and malathion residues by a chemical-specific potency factor of 61[22]. A further assumption was made of 100% oxon conversion for bensulide/disulfoton and 10% oxon conversion for malathion. The results of this sensitivity analysis indicate that oxon contribution to overall cumulative risk is relatively small.

[22] The value of 61 was extracted from the malathion risk assessment where RBC ChE data from malathion and malaoxon were evaluated.

d. Results

The results of the residential portion of the cumulative risk assessment are relatively straight-forward to interpret. In summary, the 2006 Updated OP residential assessment assumes a worst case combination of all OP residential uses and reflects worst case pesticide use information. All resulting MOEs (dermal, incidental oral, and inhalation) associated with all residential uses of the OP pesticides are greater than 100 (lowest MOEs are approximately 150) and therefore not of concern.

Inhalation exposures resulting from the indoor uses of DDVP are a major contributor to residential exposures. This is the only remaining indoor use for OPs. Dermal risk increases for a portion of the summer months. These risks are attributed to application pattern information for the trichlorfon lawn scenarios. Risks resulting from incidental oral hand-to-mouth contact are not of concern.

Table I.G-2 Input Parameters Used in the Exposure Models: Bias, Assumptions, Uncertainties, and Strengths.

Model	Input Parameter	Bias*	Assumptions, Uncertainties, or Strengths and Other Comments
Exposure Model for Residential Pathway (Rex)	Human Activity Pattern	+ = upward ~ = neutral - = downward	

Lawn Exposure	Unit Exposure: push-type rotary spreader (mg exposure per amount of active ingredient applied)	~	Assumptions/Uncertainties 1. This unit exposure is based on 30 replicates consisting of individuals using a push-type rotary spreader. A number of clothing scenarios are possible to be generated from these data. In this assessment short-sleeved shirt and short pants were assumed. This may overestimate exposure as large portion of exposure is to the lower legs. Although a surrogate compound was used, exposure is believed to be more influenced by the type of equipment used rather being chemical specific. OPP has high confidence in these data. 2. A lognormal distribution was selected. 3. Assumed gloves are not worn. Survey data do indicate that some residential handlers use gloves. Because consumers are unlikely to use, remove and care for PPE in the manner of professionals, it is unclear what impact this may have on actual use. 4. The surrogate compound (dacthal) used in the exposure study may be dustier than the granular formulations of the OP compounds assessed. This factor increases confidence that this variable will not underestimate exposure.
	Area treated (square feet)	- to ~	Assumptions/Uncertainties 5. A difficult variable to estimate. However, the assumption is reasonable given the application equipment used. Although, may underestimate areas that have larger lawns (midwest), margins of exposure are large.

	Dermal Contact Transfer	~ to +	6. Adults: activities performed with tank tops and short pants, lognormal distributions may be reflective of study design rather than actual activities (choreographed) 7. Children: Includes above scripted activities and a range of non scripted activities. Non-scripted activities lognormal distribution may be influenced by use of a non-toxic substance (not a pesticide) 8. Assumes all adults and children living in households being treated with lawn care products are exposed (enter treated area).
	Turf Residues: dermal	~	9. Chemical specific data reflect a range of high values (e.g., immediately after application) and influenced by watering-in and rainfall.
	Turf Residues: hand-to-mouth	~ to +	10. Based on surrogate data. Lone OP in surrogate data had the lowest transfer. Assumption of total residue replenishment with each contact is expected to overestimate exposure.
	Frequency of hand-to-mouth events	~ to +	11. Based on video-observations of children situated indoors. Active play outdoors may result in lower hand-to-mouth frequencies.
	Duration on lawn	~ to +	12. For children, the value is time spent outdoors in addition to time spent on lawns. Does not account for survey responses of individuals that did not play on lawns or go outside.
Public Health	Drift	~	13. Distribution of aerial and ground equipment values
	Population Exposed	~ to +	14. Assumes a large percentage of the population being exposed (based on those having lawns).

Home Garden	Applicator: Small Tank Sprayer	~ to +	15. This unit exposure is based on 20 replicates. A number of clothing scenarios are possible to be generated from these data. In this assessment short-sleeved shirt and short pants were assumed. This may overestimate exposure as large portion of exposure is to the lower legs and upper arms. Although a surrogate compound was used, exposure is believed to be more influenced by the type of equipment used rather being chemical specific. OPP has high confidence in these data. 16. A lognormal distribution was selected. 17. Assumed gloves are not worn. Survey data do indicate that some residential handlers use gloves. Because consumers are unlikely to use, remove and care for PPE in the manner of professionals, it is unclear what impact this may have on actual use. confidence in these data
	Applicator: Granular	~ to +	18. This unit exposure is based on 15 replicates. Chemical specific data. Used study assessing exposure while treating shrubs which had higher unit exposures than for flowers. 19. A lognormal distribution was selected.
	Area treated: ornamentals	~ to +	20. Assumes all plants are treated.
	Area treated: vegetables/fruits	~	21. A lognormal distribution of a well studied variable.
	Postapplication: vegetables/fruits	~ to +	22. Contact values represent a wide range of activities. All plants are assumed to be treated.
	Frequency of applications	- to +	23. Based on survey responses to use of insecticides. Not chemical specific.

	Plant residues	~	24. Regional and chemical specific
Indoor Air	Residues	~	25. Chemical specific
	Reduction in air concentration based on presumed use of smaller strips than in above residue study	- to ~	26. Proportional reduction is an assumption
	Duration	~	27. Use of CHAD consisting of several time activity surveys.
	Population Exposed	~ to +	28. Values based on use of all pest strips, not just those containing specific active ingredient.
Pet Treatments	Applicator	~	29. Chemical/formulation specific data. Number of pets and pet weights reasonable based on an “n” of 148 pets.
	Postapplication	~	30. dermal contact value, from studies in which there was substantial contact 31. Chemical specific fur residue data 32. Video-analysis of children in contact with pets. However small n (3). 33. Best available at this time
Calendex	Input parameter are describe above		34. confidence in these data

4. Regional Drinking Water Exposure Assessments

Cumulative OP exposure from drinking water is generally orders of magnitude less than exposures from food sources in the US. The exception is a brief period when estimated exposures from drinking water in south Florida (high exposure scenario representing Region A) peak as a result of OP use. The drinking water exposure assessment is presented in detail in Section I.E of this document. This section characterizes the results of the regional water exposure distributions, the basis for its conclusions, and identifies assumptions and approaches to the assessment that might impact the level of certainty in the results.

The regional drinking water exposure scenarios represent areas where combined OP residues in drinking water are likely to be among the highest within the region as a result of total OP usage and vulnerability of the drinking water sources. By focusing on high potential exposure scenarios, EPA is confident that if the regional cumulative risk assessment finds that exposure in drinking water does not exceed levels of concern in these vulnerable areas, it will not exceed levels of concern in other areas.

Identifying high combined OP exposure scenarios is not an exact science. A comparison of the estimated concentrations from individual OPs with available monitoring shows that, in each region, levels of one or more OP pesticides detected in monitoring studies are greater than that estimated by the cumulative water assessment. In the same region, estimates of other OP pesticides are similar to or greater than detections found in monitoring studies (see Appendices III.E.1 and III.E.3 and regional assessments in II.A through II.G in the 2002 OP CRA for detailed comparisons). Although the potential exists that peak water concentrations for one or more OP pesticides may not be captured in the drinking water exposure approach (see Section I.E), the impact on the contribution from water to the overall cumulative risk assessment is anticipated to be small because it is intended to capture areas of highest combined OP exposures.

a. Regional Scenario Sites

Each region in the assessment is represented by a geographic area with a high potential for cumulative exposure to OPs in drinking water. The vulnerable drinking water sources represent areas with relatively high usage of multiple OP pesticides coinciding with surface water sources of drinking water that are vulnerable to runoff. Based on characteristics of the OP pesticides and available monitoring data, the

Agency determined that ground water sources of drinking water will have lower OP residues than are found in surface water.

Because OP usage varies within the region, the evaluation focused on the areas of highest use, based upon the crops grown, which OP(s) are used on these crops, how much OP pesticides are applied and when they are used. Since the purpose of the assessment is to identify the impact from multiple OPs occurring in water in the same area, the areas selected for the assessment do not necessarily represent the highest exposure of a single chemical, but rather the highest multiple OP exposure within the region. Since OP use may vary from year to year and cropping and usage patterns may change, some areas in other parts of the region may have greater water exposure in a given year.

Because OPP considers both total OP usage and vulnerability of the drinking water sources, the site selected may not necessarily coincide with the highest OP use area in the region or the area where runoff alone is greatest. For instance, the highest OP use areas in the Northwest region (Region B) are in central and eastern Washington and in southeast Idaho. However, because of low rainfall, few surface-water intakes, and irrigation-dominated agriculture, OP use in this area did not necessarily pose the greatest risk to drinking water sources. Instead, the surface-water sources of drinking water in the Willamette Valley were potentially more vulnerable, despite lower OP usage.

b. Drinking Water Sources

OPP adapted available tools to provide daily distributions of OP levels in water for incorporation into the probabilistic cumulative exposure assessment. While these tools have provided OP distributions that are, in many cases, comparable with available monitoring data in the same or nearby locations, assumptions regarding the nature of the drinking water source and watershed influence the estimated distributions.

The index reservoir modeled with PRZM/EXAMS is based on an actual reservoir in the Midwest. As such, it best represents potential transport to similar drinking-water sources in high rainfall areas of the eastern US. It is less representative of reservoirs in drier parts of the west, where inflow and outflow are artificially managed. The reservoir scenario will not necessarily capture the magnitude of peak concentrations following storm events in rivers and streams; long-term average concentrations in a reservoir may be greater than in streams because of differences in the residence time for water in these water bodies.

PRZM is a field-scale model which provides edge-of-field estimates of pesticide loads in runoff into a reservoir simulated by EXAMS. In order to account for the relative contributions of each field to the reservoir, EPA used a cumulative adjustment factor (a combination of the fraction of the total watershed area in crops with OP uses and the fraction of acres treated by each OP on each crop) to adjust the resulting reservoir concentrations calculated by EXAMS.

PRZM does not account for location in the watershed: all fields are assumed to be uniformly distributed within the watershed, with runoff going directly into the reservoir. Runoff from fields representing the application of each OP to a different crop follows the same path length in the treated field and empties directly to the reservoir. In some instances, this may overestimate the contributions of OP pesticides applied to crops grown at a distance from the water body.

Each crop use simulated in PRZM assumes that the entire area of the watershed planted in the crop consists of a single soil. In each of the regions, OPP used data for local soils on which the crops are grown. When possible, the soil selected for each scenario was a benchmark soil that was prone to runoff (classified as hydrologic group "C" or "D" soils). While OPP attempted to simulate soils most prone to runoff, we also looked for important local soils for which sufficient data are available, and which are known to be used to grow the crops of interest. The scenarios represent soils prone to runoff that are known to support the crops being simulated. While an assessment using a single soil assumes that each part of the watershed will be equally vulnerable to runoff, areas of higher and lower runoff vulnerability will exist in an actual watershed.

Because the application rates, frequencies, and timing are held constant, the simulations over multiple years evaluate the impact of the variability in precipitation on the amount of pesticide that reaches surface water. Because weather data spanning 24 to 36 years is available for many locations across the country, PRZM and EXAMS can account for OP runoff from a wide range of weather patterns not otherwise possible with monitoring studies that span relatively few years.

c. Usage, Cropping Areas, and Acre Treatments

The assessment used typical application rates and frequencies for each OP-crop combination. This assumes that all applications were made at this typical rate and frequency every year. Using typical application rates and frequencies may underestimate water

concentrations in years when pest pressure is higher than in the reported years and may overestimate in years when lower amounts of pesticide is used. Given the range in crops and pests treated by OP pesticides in each region, it is more likely that only some of the OP pesticides might be applied at higher than typical rates in a given year while others may be applied at lower rates.

The extent to which the differences in rates from typical to maximum would be reflected in the OP cumulative distribution depends on a number of factors, including timing of application relative to runoff events and relative potency of the pesticide. In the 2002 OP CRA, EPA compared estimated cumulative distributions using typical rates with those estimated using all maximum rates. Peak concentrations (at the 95^{th} percentile and above) using maximum rates were no more than 2 to 4 times greater than cumulative concentrations estimated with the typical rates (see Appendix III.E.11 in the 2002 OP CRA).

The regional percent crop area (PCA) factors are based on large-scale hydrologic units (average area >1000 square miles) that generally span multiple counties and may contain several watersheds that supply drinking water intakes. These PCAs aggregate county-level USDA AgCensus data and assume that the cropping area is uniformly distributed. However, cropping intensity is variable and smaller watersheds, including those capable of supporting drinking water supplies, may have a much different (higher or lower) percentage of crop land than the rest of the large basin. The net effect can result in concentrations that are either higher or lower, depending on the scenario location and crops. To address this in the OP CRA, OPP used crop acreages specific to the counties surrounding the exposure scenario locations to represent crop acreages in the drinking watershed.

The typical application rates and percent acres treated derived from state-level data (or NASS reporting districts) also assume uniform use practices across the state. However, an uneven distribution of application rates and percent acres treated is expected in response to differing pest pressures. This assumption will underestimate areas where pest pressures may dictate a higher percentage of acres treated in a given year; similarly, it will overestimate areas where low pest pressures will require fewer acre treatments. The extent to which this will impact the exposure estimates will vary depending on the percent acres treated and on the potential year-to-year variability in potential acres treated. EPA used an average over 3 to 5 years to reduce the chances of selecting data for an abnormally low or high use year. The impact will be greater for single chemicals than for multiple OP use in a watershed.

d. Timing of Application

OPP used USDA crop profiles and other crop production publications to establish a time frame for making the applications of the pesticide on a particular crop (application window). The length of the window doesn't necessarily reflect the range over which a pesticide will be applied in a particular year, but the year-to-year variation in the application dates over time. Thus, in any given year, the timing of application may be clustered within a shorter time-frame than suggested by the application window. However, because of weather and other environmental factors, the timing of intensive pest pressure and/or OP application may vary across the window.

The date of application can affect the predicted concentrations, depending on how close the pesticide application coincides with rainfall events in any given year. To evaluate how this may impact the OP cumulative distribution, where multiple pesticides are applied at different dates, OPP varied dates of application across the active window for each OP-crop combination in two regions (A and D; see Appendix III.E.11 in the 2002 OP CRA for details). The impact of varying dates of application was most evident at the extremes in the distributions. The ratio in maximum cumulative concentrations between the lowest and highest estimates ranged from 5 to 6. For 99th and lower percentiles, the ratio between lowest and highest values was two or less. This analysis only looked at the cumulative OP distribution and did not evaluate variations in individual chemical distributions. In both regions, the cumulative distribution generated at the beginning of the application window and used for the regional assessment was less than the maximum estimated distribution.

In the absence of data to show otherwise, OPP assumed that all of the pesticide applied on a particular crop is done on the same date. While this may be an unreasonable assumption for a large watershed, it is not unrealistic for the size of the watershed used in this assessment. This assumption may result in higher peaks, but similar overall average concentrations than if applications are spread out over time. The resulting estimate of exposure may result in a small overestimation bias in the results that will be greater in large than in small watersheds. The degree to which a difference is seen depends on a number of factors, including the mobility and persistence of the pesticide and the timing of applications in relation to runoff-producing rainfalls.

e. Water Treatment Effects

At the time of the 2002 OP CRA, the Agency had evidence to indicate that a number of OP pesticides are likely to transform to oxons by oxidation during water treatment, through chlorination or similar disinfection treatments. Limited data also suggested that the oxons may be more toxic than the parent OP. Since then, EPA has gathered additional information to confirm which OP pesticides will convert to oxons as a result of chlorination and whether the resulting oxons may be stable for sufficient periods of time (for least 24 to 96 hours) to move through the distribution system. The results are summarized in Section I.E, Table I.E-2).

Those studies confirm the potential for the formation of stable oxons as a result of standard drinking water treatment, but do not provide enough information to quantify the rate of formation and decline of the oxons in treated water. To assess potential impacts and to determine whether additional information is needed, OPP assumed that any transformation due to chlorination results in the conversion to a product of toxicological concern. Thus, EPA assumed that all OP pesticides that form oxons, sulfoxides, or sulfones were transformed into those products as a result of oxidation. Where the transformation is less than complete, and where non-toxic products are also formed, this assumption will overestimate the ultimate drinking water exposure. While limited information suggests that some OP pesticides may be transformed and removed from treated drinking water, sufficient information is not available to quantify this for all OP pesticides. Thus, OPP did not assume that any of the other OP parent pesticides would be removed.

OPP assumed that the sulfoxide and sulfone products are equal in toxicity to the parent. Limited information is available on the relative toxicity of the oxons. For this 2006 update, the Agency used specific oxon adjustment factors for three OP pesticides (dimethoate, chlorpyrifos, and methyl parathion) based on available information. For the remaining OP pesticides, EPA used oxon adjustment factors of 10X and 100X to consider upper bound estimates of potential oxon potency.

The highest estimated cumulative OP concentrations in drinking water occurred in Region A (south Florida). The major contributors to the cumulative exposure in this region were phorate (including sulfide and sulfone) and ethoprop, which do not form stable oxons. Even with the 100X oxon adjustment factor, the peak concentrations did not change (see Table I.E 5 in Section I.E). Therefore, the Agency used

this as basis for comparison for the rest of the oxon-adjusted distributions.

With a 10X default oxon adjustment factor, the peak concentrations in most of the regional distributions increased by no more than 25%. All of the regional distributions remained well below the peak distributions of Region A. When the 100X oxon adjustment factor was applied, peak concentrations in Regions C, E, F, and G shifted upwards in relation to that of Region A. However, only the distribution for Region C increased (by 30 to 50X) to the extent that it surpassed the distribution of Region A (Figure I.E-3 in Section I.E). The major contributor to the increase is the oxon of methidathion. The modeled exposures for methidathion, which is used on orchard crops, has a maximum of 0.15 ug/l (ppb) and a 99th percentile concentration of 0.06 ppb. These concentrations are comparable to maximum reported detections from available monitoring studies in CA. Laboratory studies documented in Appendix II.E.1 indicate that the assumptions of complete conversion, with the oxon being stable for at least 72 hours, are reasonable. Although EPA does not have data on the toxicity of the oxon of methidathion, the Agency believes that the actual differences in relative toxicity are likely to be less than 100X. While the assumptions applied to the oxon characterization are conservative, the data are insufficient to make a quantitative determination at this point. This uncertainty can be reduced with data on the toxicity of the oxon which the Agency will require to be submitted. Appendix II.G.2 provide more detail regarding the potential for oxon exposure in drinking water.

f. Results

Estimated maximum concentrations for individual OP pesticides in the regional drinking water exposure scenarios were in the single- to sub-parts per billion range. In a few instances, estimated exposures were less than levels reported in monitoring. In some instances, the underestimates resulted when the Agency shifted from conservative assumptions (maximum application rates, 100% crop treated), as discussed above. In most instances, the monitoring reflected areas outside of the cumulative assessment area or contributions from uses that have been phased out. In other instances, the estimated exposures were greater than levels reported in monitoring. Because the OP CRA focused on co-occurring OP residues, estimated concentrations for individual OP pesticides may not reflect maximum potential exposures for that pesticide. However, the scenarios should reflect maximum combined exposure for the regions. An evaluation of the monitoring data, along with information on OP use, drinking water intake locations, weather data, and runoff vulnerability support this assumption.

These estimates were generally within the range of known monitoring data. The cumulative OP concentrations, adjusted for relative potencies to methamidophos equivalents, reflect the estimated combined exposures from co-occurring OP residues in potential high-exposure scenarios across the country. The temporal profiles for these exposures tend to show one or more yearly peaks that coincide with runoff events shortly after application. For most of the year, the concentrations are orders of magnitude lower than the estimated peaks.

The one notable exception is in Region A (Florida), where estimated peak concentrations of total phorate residues (parent plus sulfoxide and sulfone transformation products) from use on sugarcane resulted in MOEs near 80 for children 1-2 years old at the 99.9th percentile of exposure for a brief period (16 days). The major contributors to this peak load are the sulfone and sulfoxide transformation products of phorate, primarily from use on sugarcane. These transformation products form in the environment and, based on EPA's 2001 Interim Reregistration Eligibility Decision for Phorate (http://www.epa.gov/oppsrrd1/REDs/phorate_ired.pdf), are expected to be equal in toxicity to phorate. OPP had monitoring data to make comparisons for a number of OP pesticides, but did not have monitoring data for the phorate sulfones and sulfoxides. However, based on the relatively short persistence (half-lives on the order of days to weeks), the nature of the drinking water sources in south Florida, and laboratory studies on chlorination effects on the phorate residues, EPA expects actual exposure from phorate residues to be lower than estimated. This drinking water exposure scenario is analyzed in more detail in Appendix II.G.3. While the actual extent to which actual exposures would be less than estimated is not known, EPA expects that resulting MOEs will be above 100. This uncertainty can be reduced with targeted monitoring for phorate, phorate sulfoxide, and phorate sulfone in both the source water (at the intake) and treated water for roughly five CWS in Palm Beach County and two around Lake Okechobee which the Agency will require to be submitted.

5. FQPA 10X Factor for the Protection of Infants and Children

The FQPA (1996) instructs EPA, in making its "reasonable certainty of no harm" finding, that in "the case of threshold effects, **an additional tenfold margin of safety** for the pesticide chemical residue and other sources of exposure shall be applied for infants and children to take into account **potential pre- and postnatal toxicity and completeness of data with respect to *exposure* and *toxicity* to infants and children**."

Section 408 (b)(2)(C) further states that "the Administrator may use a different margin of safety for the pesticide chemical residue only if, on the basis of reliable data, such margin will be safe for infants and children." The following discussion synthesizes information discussed in previous sections of this characterization and information from the hazard, food, water, and residential chapters of the OP CRA to inform FQPA 10X factor for infants and children. Overall, the Agency believes that there are quality data and scientifically supportable methods to account for specific exposure and behavioral patterns of children. Because characteristics of children are directly accounted for in the exposure assessment and the Agency's methods are not expected to underestimate exposure to OPs, evaluating the potential for increased toxicity of juveniles is the key component in determining the magnitude of the FQPA factors in the CRA.

The previous sections of this risk characterization describe the data sources and models used to generate the food, drinking water, and residential exposure assessments. Overall, there is a high degree of confidence in the exposure data and methodologies used when assessing cumulative risk to children from food, drinking water and residential exposure. The cumulative exposure assessments are considered to be protective of children and do not understate risk.

The Agency has retained the 10X factor for most of the OPs in the CRA. The Agency has refined this factor for 10 OPs (and omethoate) that were identified in the revised CRA (USEPA, 2002) as OPs that may be non-negligible contributors to the cumulative risk and had high quality repeated dose comparative cholinesterase data in juvenile and adult animals. As part of the evaluation for these OPs, the Agency considered both pre- and post-natal toxicity studies and concluded that in pre-natal studies dams exhibit more cholinesterase inhibition than fetuses and that post-natal studies provide a more robust dataset for evaluating age-related sensitivity. The Agency has used refined BMD methods for quantifying the relative sensitivity between juvenile and adults. The Agency believes that the refined FQPA factors are protective of infants and children in that high quality data from sensitive populations were used along with peer-reviewed dose-response methods that provide quality statistical fit the toxicity data.

6. Matching Timeframe of Exposure with Timeframe of Toxicity

a. Background

The cumulative risk assessment guidance describes key principles for conducting these risk assessments. One such principle is the need to consider the time frame of both the exposure (e.g., When does exposure occur? What is the exposure duration?) and of the toxic effect (e.g., What are the time to peak effects and the time to

recovery? How quickly is the effect reversed?). In the case of the OPs, exposures can be from food, water, and/or residential pathways. Patterns of exposure are variable and as described in detail in the CRA can differ by region, age, and individual behavior. In general, exposure to OPs, and thus potential cholinesterase inhibition, can be acute (single day) for some food commodities or longer in duration (several months) for some residential uses.

During the data evaluation phase of the cumulative risk assessment, OPP elected to use only those toxicology studies that resulted from exposure of rats for 21 days or longer where cholinesterase inhibition in the laboratory animal is not changing with time. OPP defines this point where continued dosing at the same level results in no further increase in enzyme inhibition as steady state. This choice was made for a number of reasons. Various toxicokinetic and toxicodynamic factors influence an individual OP's time to peak effect of inhibition, persistence of action following acute exposure, and the duration of exposure required to reach steady state inhibition. Following exposure to an OP, regeneration of cholinesterases to pre-exposure levels occurs in the time scale of days to weeks, not a single day, making the exposed individual potentially more vulnerable to subsequent exposures during that period. Because of the many agricultural uses of OPs and the resulting residues that occur in food and water, and also the application of OPs in homes, the likelihood of being exposed to an OP with no prior recent exposure to OP(s) is considered to be small.

Conceptually, a multi-chemical, multi-pathway pharmacokinetic or biologically based model (eg, PBPK model) would be better able to account for the dynamic nature of environmental exposure(s) and of cholinesterase inhibition, recovery, and regeneration. However, as described in detail below, at this time, such a model does not exist. Based on the understanding that following repeated exposures cholinesterase inhibition increases and that reversibility for OP-induced cholinesterase inhibition requires several days to weeks, the decision to use steady state measures of cholinesterase inhibition as the basis for OPs RPFs and the PoDs for the index chemical is a reasonable approach.

In previous versions of the OP CRA (2001, 2002) the Agency has presented exposures and risks associated with exposure durations of a single day and of rolling averages ranging from 7 to 21 days in duration. As shown in the 2002 Revised CRA, the magnitude of risk does not change significantly between the 7, 14, and 21 day rolling averages. Moreover the results of the 7, 14, and 21 day rolling averages provided redundant information. The 21-day analysis was

selected over the 7 and 14 analyses for the 2006 Update as 21 days provides a better match to the toxicity data used to derive the RPFs and points of departure compared to the 7 and 14 day rolling average analyses.

In the 2006 Update, the Agency has elected to present the single day and 21-day rolling average analyses for food exposure and only the 21-day rolling average analysis for water, residential, and multi-pathway scenarios. The Agency has previously stated that the actual risk to the OPs may lie between the results of the single day and rolling average analyses. This conclusion was based in large part on the assumption that peak high end exposures could come from multiple pathways, particularly food and residential. In the last few years, the in home uses of chlorpyrifos and diazinon and many of the uses of DDVP residential uses have been cancelled. In the 2006 Update, exposure to DDVP is the major contributor to residential risk. Unlike other OP residential scenarios, indoor exposure to DDVP pest strips and pet collars is continuous for the effective life of the product (up to 16 weeks). DDVP pest strips and pet collars are constantly emitting sources that dissipate over the duration of use. For this reason, the 21 day analysis more appropriately addresses DDVP exposure than the single day analysis.

As part of the 2006 Update, the Agency reconsidered whether the single day, the 21-day rolling average, or the combination better describe the cumulative food risk to the OPs. In this reconsideration, the Agency evaluated information regarding the time to recovery for OPs, biomonitoring studies, and the assumptions included in the single day and 21-day rolling average food risk assessments. The Agency has concluded that the 21-day rolling average approach is more appropriate analysis as it better matches the toxicity data used to derive the RPFs and PoDs. Due to the conservative assumptions included in the CRA the 21-day rolling average approach is not expected to undestimate residual ChE inhibition which could occur between OP exposures and thus provide a reasonable estimate of cumulative to the OPs.

The following section describes the uncertainties and strengths associated with the current approach. This section also describes the current limitations in data and software to fully characterize the dynamic nature of exposure, effect, and recovery for this common mechanism group.

b. Information from Monitoring Studies

Examination of the rat data indicates that for most pesticides, cholinesterase inhibition reached steady state by approximately 21 to 30 days after the start of dosing. After that point, little change occurred in the degree of inhibition resulting from continued administration of the dose for a longer period. The application of a steady state approach is predicated on the assumption that the extent of cholinesterase inhibition on any given day reflects the balance between prior exposures and the extent of recovery experienced. The processes of inhibition and recovery are balanced in the steady state rat data. The degree to which this balance of inhibition and recovery is achieved in human populations depends on the magnitude and frequency of OP exposures. The major distinction between the steady state data from the rat studies and the likely inhibition in the exposed population is that the actual dose to the rat on any day and on preceding days is known. In the human population, the prior exposures can not be known with certainty. However, as demonstrated by the current exposure assessment, the prior exposures may be either higher or lower than for the current day.

There is a body of evidence that indicates a sizeable proportion of the US population has a fairly constant background exposure to OPs. This is evident from the results of the NHANES III in which 82% of people who provided urine samples for analysis were found to be positive for trichloropyridinol, a metabolite of the OPs chlorpyrifos and chlorpyrifos-methyl (Hill et al., 1995). Further examination of the NHANES III data indicate that a sizeable proportion of the population have metabolites in their urine that are not compound specific, but are associated with other OPs. Preliminary analyses of data collected under the auspices of NHEXAS also indicate that metabolites from a variety of OPs are found in urine from populations of adults and children sampled around the US. In addition, examination of NHANES biomonitoring data from 1999-2000 and 2000-2001 suggests that a similarly sized fraction of the U.S. population have OP metabolites in their urine. Although the true pattern of human exposures is not known, biomonitoring studies support the idea that humans are regularly exposed to OPs and that use of the rat toxicity studies in which rats are exposed to OP pesticides on a daily basis is not an unreasonable approach.

In a recent study by Lu et al (2006), over a 15 day period, school age children were given conventional and organic diets. Their urinary metabolites were measured during the periods of conventional (days 1-4 and 10-15) and organic (days 5 -9) diets. The urine of all 23 children contained the biomarkers for malathion and chlorpyrifos when enrolling

in the study. Concentrations of OP metabolites in urine decreased significantly during the period of organic diet and then rose again during days 10-15 of the conventional diet. The small sample size of this study precludes extrapolation to larger populations but the regularity of OP metabolite detections in the children's urine supports the approach of using steady state ChE data to estimate cumulative risk to the OPs.

c. Food Exposure Assessment

OPP's assessment considers the potential risk from single day (acute) exposures across a year and from a series of 21-day rolling averages across the year. In DEEM Calendex software used here, one diary for each individual in the CSFII is selected to be paired with a randomly selected set of residue values for each food consumed. In the single day analysis, a set of exposures from OPs in foods is developed and arrayed as a distribution from high to low exposures. In the 21-day analysis, a rolling average of exposures for each individual is calculated. Both of these analyses assume that exposure days are independent within an individual and the exposure from one day is unaffected by the previous days exposure. For example, the residues in any watermelon or apple juice consumed today are assumed to be independent of the residues in any watermelon or apple juice consumed during subsequent days In reality, both the foods eaten and corresponding residues on any given day may not be independent of preceding days to the extent that individuals consume bulk items such as juice, bunches of grapes, or bags of produce or left-overs that may have the same level of residues over multiple days. As a result, exposure from such "bulk" items may be under estimated at the high-end in the single day and 21-day rolling analyses to the extent that a high end residue for a given food item may be selected on one day, but not resampled on the subsequent days during which that item is consumed. As result, these assessments may be biased downward with respect to the risk estimates developed, although the magnitude of the error is not known.

The use of the CSFII data in the 21-day rolling average consists of a repeated random redraw of the two available days of consumption data for each person in the data base over a 21 day period. This process maintains the integrity of the data for individuals, including, to the extent possible, any information defining patterns of diet peculiar to them. However, the redraw process results in the implicit assumption that every individual in the CSFII consumes a diet that is limited to the records in the diaries repeated randomly across the year. As a result, the variability likely to occur in the diet is not fully expressed in the current risk assessment. This factor is expected to reduce the range of

exposures to which any particular individual can be exposed by limiting the number of commodities and pesticides possible to those reported in the two daily diaries. This factor is anticipated to introduce an upward bias into the exposure assessment in comparison to actual longitudinal consumption patterns. Since only a small percent of food diaries generate high exposure, individuals having those diaries will have higher expected exposure over a 21 day period if they have the same two diets over this period, than if they are allowed to draw on other diets. In the long term, development of longitudinal consumption data could add significant value on this issue but such data are not available at this time.

For the two key assumptions discussed here (independence of residues across days and the use of CSFII where only two diaries per individual are available) provide a potential underestimate and overestimate of risk, respectively, at the high end percentiles. The magnitude of the potential bias is unknown. However, these upward and downward biases are not expected to significantly affect the risk estimates at the upper ends of the distribution.

d. Water Exposure Assessment

Pesticide concentrations found in drinking water are in large part determined by the nature of the pesticide, the amount, method, timing and location of pesticide application, hydrologic and environmental factors, and amount and timing of rainfall in relation to application. Concentrations of pesticides in drinking water sources are related to each other in time. Particularly in surface water, pesticide loads tend to move in relatively quick pulses (lasting a few days to a few weeks) in response to runoff events after rainfall. Thus, high exposures tend to occur together in time. This creates distinct time series patterns that follow seasons (Figures I.E-2, I.E-4, and I.E-5 in the Drinking Water Section, I.E, illustrate this pattern). The drinking water exposure traces in the cumulative graphs reflect the seasonal patterns expected to occur for pesticides in water. Seasonal patterns are also evident in available drinking water monitoring studies.

The trends observed from both the single day and 21-day rolling averages reflect the kind of exposure trace one would expect from monitoring (a) samples every 24 hrs and (b) daily samples averaged over 21 days in that pesticide concentrations in surface water bodies are likely to exist at some low baseline level and then spike during/after a runoff event. The magnitude and width of that residue spike depends on both how much pesticide is present in the field and how extensive and intense the storm event happens to be. Two scenarios have been identified as potential contributors to risk for phorate (including the

sulfoxide and sulfone) and methidathion oxon where MOEs are lower than those for food for short periods of time in specific localities. As described in previous sections, the risks calculated for these scenarios are likely the result of compounding conservative assumptions. The Agency is taking steps to further evaluate these risks, including targeted drinking water monitoring for phorate (including the sulfoxide and sulfone) and animal toxicity data for methidathion oxon.

e. Residential Exposure

The inhalation pathway is the major contributor to overall residential exposure. Residential inhalation exposure primarily results from indoor post-application exposure to DDVP pest strip and pet collars. Unlike other OP residential scenarios, indoor exposure to DDVP pest strips and pet collars is continuous for the effective life of the product (up to 16 weeks). DDVP pest strips and pet collars are constantly emitting sources that dissipate over the duration of use. For this reason, the 21 day analysis more appropriately addresses DDVP exposure than the single day analysis. Further, since DDVP is a major contributor to the overall residential exposure, the 21 day analysis also is more suitable to assess overall residential exposure and risk.

f. 21-Day Rolling Average Approach Compared with Peak Exposures in Food

Typically, OPP tries to match the duration of exposure with the duration of the toxic effect of interest. Compared to the 24 hour, single day exposure estimates, the 21 day rolling average mode of exposure analysis better matches the steady state data used to derive the RPFs and PoDs. Moreover, based on the results of biomonitoring studies that suggests humans are regularly exposed to OPs, use of steady state toxicity information paired with 21-day rolling averages better approximates human exposures. Nevertheless, EPA is concerned with peak, acute exposures. The Agency has conducted a sensitivity analysis where cumulative risks from single day food exposures were calculated using RPFs and PoD derived from acute toxicity studies in rat. This sensitivity analysis is described in detail in Appendix II.G. 4. The purpose of this analysis was 1) to better understand the relationship between the results reported for the single-day and 21-day rolling average analyses compared with the steady state hazard data and 2) to ensure that the CRA was protective of potential peak exposures to multiple OPs in food.

Briefly, the Agency collected acute toxicity information for those OPs that most significantly contribute to food exposure for children 1-2 and 3-5 years old. Acute RPFs and PoDs were calculated for these OPs.

Steady state toxicity information were used for all other OPs (and as such, the acute sensitivity analysis considered an overestimate of acute, cumulative risk to the OPs). The acute sensitivity analysis is meant only as a sensitivity analysis and is not intended to replace the results presented in I.C and I.G for the 21-day rolling average analysis.

Table I.G-3 Cumulative Food Assessment MOEs at the 99.9th Percentile of Exposure.

	21-Day Analysis Based on Steady State Endpoints	Single-Day Analysis Based on Steady State Endpoints	Single-Day Analysis Based on Single-Day Endpoints
Children 1-2 yrs	110	30	52
Children 3-5 yrs	99	34	63
Adults 20-49 yrs	280	75	130

Table I.G-4 Cumulative Food Assessment MOEs at the 99th Percentile of Exposure.

	21-Day Analysis Based on Steady State Endpoints	Single-Day Analysis Based on Steady State Endpoints	Single-Day Analysis Based on Single-Day Endpoints
Children 1-2 yrs	250	130	200
Children 3-5 yrs	300	160	250
Adults 20-49 yrs	610	290	480

Table I.G-5 Cumulative Food Assessment MOEs at the 95th Percentile of Exposure.

	21-Day Analysis Based on Steady State Endpoints	Single-Day Analysis Based on Steady-State Endpoints	Single-Day Analysis Based on Single-Day Endpoints
Children 1-2 yrs	550	440	610
Children 3-5 yrs	670	510	690
Adults 20-49 yrs	820	990	1400

In Chapter I.C, the margins of exposure (MOEs) at 95th, 99th, and 99.9th percentiles of exposure are reported for the 21-day and single-day food assessments based on steady state endpoints. These MOEs were reported for various age groups, the mostly highly exposed of which were children 1-2 and 3-5 years old. Briefly, the MOEs for the 21-day assessment are above or very close to the target of 100 at the 99.9th percentile of exposure for all age groups; the MOEs for the 95th and 99th percentiles of exposure are well above 100.

However for the single-day analyses, the MOEs at the 99.9th percentile of exposure do not reach the target value of 100 for any of the age groups; at the 95th and 99th percentiles of exposure the MOEs for all age groups are above 100. More specifically, the MOEs at the

99.9th percentile of exposure for children 1-2 and children 3-5 years old are 31 and 35, respectively. It is important to note that MOEs of 100 were reached at approximately the 99.3rd and 99.5th percentile of exposure for children 1-2 and 3-5 years old, respectively.

When the RPFs based on single-day acute endpoints are incorporated into the single-day exposure food assessment, the MOEs at the 99.9th percentile exceeded the target of 100 for all age groups except children 1-2 and 3-5 years old. The MOEs for these two most highly exposed age groups reached the target of 100 at approximately the 99.7th and 99.8th percentiles of exposure, respectively. Note that for most OPs, the steady state toxicity information was used for the acute analysis. Use of acute toxicity for the remainder of OPs would increase the MOEs and also the percentile where an MOE of 100 is reached. As such, given the conservative nature of the acute analysis, the Agency concludes that the OP CRA was protective of potential peak exposures to multiple OPs in food.

g. Physiologically-Based Pharmacokinetic Models

Physiologically based pharmacokinetic (PBPK) models, which describe the time course disposition of chemicals and their metabolites, could help assess cumulative risk and to evaluate the relationship between variable environmental exposures and dynamic biological processes. Appropriate PBPK models could quantify the cumulative toxicity that can result from multiple exposures (multiple exposures and multiple pathways) and from exposure to multiple chemicals with a common mechanism or mode of action. While these models are excellent tools, numerous input parameters are necessary for each chemical. Organ-specific thermodynamic parameters (such as tissue to blood equilibrium partition coefficients) are required for each pesticide entering the body and for each of its metabolites. Additionally, values for all of the metabolic rates governing all the biotransformation steps for each pesticide would be necessary as would information on cholinesterase inhibition and potential mixture effects.

Exploratory PBPK models have been developed for some OPs. One such model has been used to simultaneously model the disposition of ethyl-parathion, isofenphos, and chlorpyrifos and their respective metabolites (Knaack et al 2004). Another PBPK model has been developed to describe the complex pharmacodynamics of acetylcholinesterase inhibition following OP exposure, based almost entirely on *in vitro* information (Gearhart, et al., 1994). Timchalk et al. (2002 and 2006) developed a PBPK model for chlorpyrifos and and its

major metabolites in adult and pre-weanling rats. Poet et al. (2004) also developed a PBPK model for diazinon. Van der Merwe et al. (2006) focused their PBPK efforts on dermal absorption of ethyl parathion, fenthion, and methyl parathion. Recently, Evans et al. (2004) presented preliminary results of a PBPK model focused on dermal exposure to malathion.

At present, these types of data/information on the majority of the OPs, including some considered to be key exposure contributors (e.g., acephate, methamidophos, DDVP) are not available to EPA (Knaack et al, 2004). Because PBPK modeling techniques offer good promise, continued development and testing of the models is necessary and should be pursued despite the current limitations with respect to the amount of input information required . Pharmacokinetic studies (*in vivo* and *in vitro* experiments to determine key values for pharmacokinetic parameters and the time course disposition of the compounds in the body) need to be done with many compounds to determine the key parameters of use in PBPK modeling. It is anticipated that data and methods will continue to improve and evolve as more experience is gained in this area. Although a biological or pharmacokinetic modeling approach would be preferred to determine the cumulative risk for these OPs, the input parameters for such an approach are not available. Thus, the pharmacokinetic characteristics of the OPs could not be incorporated in the dose-response assessment which would allow for a more refined estimate of the combined risk to humans. Therefore, OPP has applied simple dose addition and used an empirical curve fitting model (i.e., the exponential model) to determine RPFs and PoDs.

7. Conclusions

With the passage of the FQPA (1996), new statutory requirements for human health risk assessment of pesticide chemicals were placed on the Agency. With these new requirements came scientific challenges, included among these was cumulative risk assessment. The Agency designated the OPs as a common mechanism group in 1999 and began work to develop a cumulative risk assessment for this group. Since that time, the Agency has developed guidance, pilot analyses, preliminary and revised risk assessments. At each step in the process, the Agency engaged the public and the stakeholders and sought the advice from the FIFRA SAP. The update to the OP CRA (2006) represents a major milestone in the process of reassessing the tolerances for the OPs as part of the FQPA statutory deadline of August, 2006.

The OP CRA is a highly complex, highly refined risk assessment that uses data from multiple sources and multiple models. Because of this

complexity, no single value in the assessment should be used to independently arrive at the interpretation of the results. Instead, it is necessary to consider the results in their totality in order to appropriately interpret the results and arrive at conclusions. This OP CRA assessment reflects the completed risk mitigation measures from the single chemical assessments as of July, 2006. It presents the estimates of cumulative risks associated with exposures to OPs in food, drinking water and from residential uses. The assessment uses the 21-day rolling average mode of analysis. Contributions from various pathways and routes of exposure are arrayed separately in set of temporal or time-series plots of MOEs over a period of 365 days so that the reader can assess and evaluate -- on a pathway and/or route- specific basis -- the significant contributors to risk. This practice permits expression of the full range of values for each parameter and allows for an improved ability to interpret the complete risk picture. OPP is confident that the results reasonably represent exposures and risks from food, water, and residential use to the U.S. population.

The food component of the OP cumulative risk assessment is considered to be highly refined and to provide reasonable estimates of the distribution of exposures across the U.S. Although there are a few uses of OP pesticides on food crops that play a larger role in the results of the food risk assessment[23], evaluation of the total risk from exposure to OPs in foods indicated that the cumulative MOEs of 107 and 99 for children 1-2 and 3-5, respectively from exposure to OPs in foods do not raise a concern with respect to the 21 day rolling average period where the target MOE is 100. For the 24-hour single MOEs, cumulative MOEs of 30 and 34 for children 1-2 and 3-5, respectively, from exposure to OPs in foods do not raise a concern since the single day exposures assessment is compared to hazard endpoints based on steady state exposures which are 2-11-fold smaller (ie, more protective) than those for single day toxicity studies. In this way, the steady state hazard assessment does not directly match the single day exposure assessment. A more appropriate matching of single day hazard information with single day exposure estimates is expected, and has been demonstrated, to result in MOEs near to or larger than the target of 100. Moreover, the single day MOEs which tend to overestimate risks exceed the target MOE of 100 at the 99.3rd percentile of exposure and thus provide support of the health protective nature of the current risk assessment.

With respect to residential uses of the OPs, there are 8 OP chemicals with currently registered residential uses considered as part of this OP Update. A number of reliable data sources including both survey data and chemical specific factors from experimental studies were used to define how pesticides are used, how quickly the residues dissipate, how people

[23] These include: methamidaphos/acephate on beans, watermelon and tomato; and phorate on potato .

may come into contact with pesticides (e.g., via dermal or inhalation exposure), and the length of time people might be exposed based on certain activities (e.g., playing on a treated lawn). Seasonal applications and timing were considered and incorporated into the assessments. The risk estimates reported here provide reasonable estimates of risk associated with residential uses since the principal risk contributor (DDVP pest strips) are well-modeled and use experimentally-derived data. The results of the residential risk assessment indicate that remaining uses of OPs in a residential setting are anticipated to provide only minor contributions to the cumulative risks from OP pesticides, with the exception of pet collars and pest strips containing DDVP. However, the mitigation actions which have recently been agreed to and formalized are expected to substantially reduce estimated exposures and associated risks and significantly reduce the contribution of DDVP to the cumulative risk assessment. As a result of these agreements, risks associated with the DDVP pest strips are now considered to be below OPP's level of concern.

As with the residential assessment, exposures through drinking water are incorporated into the cumulative exposure assessment on a regional- and source water-specific basis. They are intended to represent exposures from vulnerable drinking water sources resulting from typical OP pesticide usage and reflect seasonal variations as well as regional variations in cropping and OP use. Since each regional assessment focuses on areas where combined OP pesticide exposure is likely to be among the highest within the region as a result of total OP usage, exposure and risk estimates presented in the OP CRA are highly conservative and only applicable to highly vulnerable sites with high OP usage. For surface water, drinking water reservoirs in small, predominantly agricultural watersheds are likely to be most vulnerable. Monitoring data are used to corroborate the modeling results and have helped confirm locations of potentially vulnerable drinking water sources. While exceptions exist, cumulative OP exposure from drinking water is generally orders of magnitude less than exposures from food sources in the US.

Available studies confirm the potential for ten OPs to form of stable oxons as a result of standard drinking water treatment. Limited information is also available to indicate that three of the OP pesticides with residential uses may also degrade to oxons. Based on sensitivity analyses conducted for oxon exposure through the residential and drinking water pathways, OPP concludes the potential for formation of oxons will not substantially alter the risk estimates provided in this assessment. The Agency believes that the assumptions applied in its oxon sensitivity analysis are conservative and that actual oxon exposures are expected to be less than estimated. However, the data are insufficient

at this point to develop and incorporate quantitative determinations of this potential in our baseline assessment.

EPA also evaluated total MOEs for all three pathways (food + water + residential) simultaneously. The MOEs at the 99.9th percentile are approximately 100 or greater for all populations for the 21 day average results from Calendex. One exception is in Region A, where drinking water exposures representing the most vulnerable CWS, results in an exposure spike where the MOEs go below 99 for almost a month for the children subpopulations at the 99.9th percentile. This spike is due to phorate sulfone and sulfoxide concentration contributions through the drinking water pathway. However, because the phorate residues break down quickly during chlorination and because the exposure concentrations represent water bodies that flow into larger drinking water supplies (resulting in both dilution and in additional degradation with travel time), this exposure estimate is likely an overestimate of actual concentrations in drinking water in this region.

The Agency has developed a highly refined and complex cumulative risk assessment for the OPs that represents the state of the science regarding existing hazard and exposure data and the models and approaches used. The Agency concludes that the risk mitigation efforts of the past several years have significantly reduced risk from OPs in the food, drinking water and from residential use in the US. **The Agency concludes that the results of the OP CRA support a "reasonable certainty of no harm" finding as required by FQPA and that the pesticide tolerances for the OPs can be reassessed.**

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II. Appendices for the 2006 Updated OP Cumulative Risk Assessment

A -1. Mitigation Summary for the OPs

Table II.A-1 Mitigation Summary for the OPs.

Decision Document	Use Site	Mitigation	Residential Uses Remaining
ACEPHATE			
9/2001 IRED	Residential Indoor Uses	**Cancelled**	Industrial buildings, institutional buildings, commercial buildings, golf courses, sod farms, fire ant and harvest ant (mound treatment), ornamental gardens
	Turf grass (except golf courses, sod farms, and post/or mound treatment for ant control)	**Cancelled**	
	Sod Farms (non- granular formulation)	Reduce maximum application rate to 3 lbs ai/A	
		Establish 3 day PHI	
	Golf Courses (non-granular formulation)	Reduce maximum application rate to 4 lbs ai/A	
	Turf - aerial application	**Cancelled**	
	Cotton- aerial application	CA and AZ: limit application rate to 1 lb ai/A	
		Rest of US: limit application rate to 0.75 ai/A	
	Greenhouse, floral and foliage plant crops, outdoor floral and ground covers	Reduce maximum application rate to 1 lb ai/ 100 gallons of water	
		Application not to exceed 0.75 lb ai/A	

Decision Document	Use Site	Mitigation	Residential Uses Remaining
	Cut flowers	Reduce maximum application rate to 1 lb ai per 100 gallons of water	
		Application not to exceed 0.75 lb ai/A	
AZINPHOS-METHYL (AZM)			
10/2001 IRED	Group 1 Chemicals: Alfalfa, succulent beans, snap beans, birdsfoot trefoil, broccoli, cabbage, Chinese cabbage, cauliflower, citrus, celery, clover, cucumbers, eggplant, filberts, grapes, melons, green onions, dry bulb onions, pecans, plums and dried plums, quince, spinach, strawberries, tomatoes	**Cancelled**	None
	Group 2 Chemicals: Cotton, cranberries, nectarines, peaches, potatoes, southern pine seed orchards, caneberries	**Cancelled**	
2006 Decision (Notice of Availability of Proposed Decision published at 71 FR 33448)	Group 3 Chemicals: Almonds, nursery stock, parsley, pistachios, walnuts	**Phased-out by 2007**	
	Group 3 Chemicals: Apples, crab apples, pears, lowbush blueberries, highbush blueberries, sweet cherries, tart cherries, parsley	**Phased-out by 2010**	
BENSULIDE			

Decision Document	Use Site	Mitigation	Residential Uses Remaining
6/2000 IRED	Low-pressure hand-wands	Restrict use to spot treatments only	Golf Courses, Lawn Care
	Use on fairways	Restrict use to 1 application during the fall season	
		Restrict use to only bentgrass fairways, in only 18 states (OH, PA, NY, MI, CT, MA, IN, IL, NJ, WV, MN, WI, VT, NH, RI, DE, MD, VA)	
	Chemigation application method	Use limited to California and Arizona	
	Use on large turf areas in parks and recreational areas, and use on ornamentals	**Cancelled**	
CADUSAFOS-No Mitigation Necessary			
CHLORETHOXYPHOS-No Relevant Mitigation Necessary			
CHLORFENVINPHOS-All Uses Cancelled			
CHLORPYRIFOS			
6/2000 Memorandum of Agreement (MOA)	Residential uses with child exposure	**Cancelled**	Ant and roach baits
	Outdoor uses with child exposure	**Cancelled**	
	Termiticides	**Cancelled**	
	Post-Construction Uses	**Cancelled**	
	Pre-Construction Uses	**Cancelled**	

Decision Document	Use Site	Mitigation	Residential Uses Remaining
	Tomatoes	**Cancelled**	
	Post-bloom uses on apples and grapes	**Cancelled**	
	Ant and roach baits	Must be sold in child-resistant packaging	
CHLORPYRIFOS-METHYL-No Relevant Mitigation Necessary			
CHLORTHIOPHOS-All Uses Cancelled			
COUMAPHOS			
8/1996 RED	Poultry	**Cancelled**	
DIALIFOR- All Uses Cancelled			
DIAZINON			
2001 MOA	Indoor and outdoor residential uses	**Cancelled**	None
7/2002 IRED	Chinese broccoli, Chinese cabbage, Chinese mustard, Chinese radish, corn, grapes, hops, sugar beets, walnuts, red beets, table beets, broccoli, Brussels sprouts, cabbage, carrots, cauliflower, collards, endive, ginseng, kale, melons, mustard, bulb onions, green onions, radishes, spinach, sugar beets, sweet corn	**Cancelled**	
	Apples, pineapples	Maximum 2 applications per year	

Decision Document	Use Site	Mitigation	Residential Uses Remaining
	Apricots, cherries, nectarines, peaches, pears, plums/prunes,	Maximum 1 application per growing season, every other year	
	Blueberries foliar application, figs, filberts (hazelnuts)	Maximum 1 application per year	
	Succulent beans, red beets, broccoli, Brussels sprouts, cabbage, carrots, cauliflower, collards, endive, kale, mustard greens, onions, succulent peas, radishes, rutabagas, spinach, tomatoes	Maximum 1 application per year	
	Caneberries	Maximum 3 application per year	
	Ornamentals	Maximum 1 lb ai/A	
		Maximum 1 foliar application per crop	
	Strawberries, melons	Maximum 1 foliar application per crop	
		Maximum 1 soil application per crop	
	Ginseng, watercress	Maximum 1 foliar application per year	
	Lettuce	Liquid and wettable powder formulations: maximum 1 foliar application per year	
		Granular formulations: maximum 1 application at plant per crop	
DICROTOPHOS			
4/2002 IRED	Cotton	Total seasonal rate limited to 1 lb ai/A	Shade trees (this is a restricted

Decision Document	Use Site	Mitigation	Residential Uses Remaining
		Limit total use based on growth stages of cotton	use tree injection application, made by professional applicators, which would not result in residential exposures)
DIMETHOATE			
2000 MOA	All residential products	**Cancelled**	None
2005 Cancellation Order (70 FR 41717)	Apples, broccoli raab, cabbage, collards, grapes, head lettuce, spinach, fennel, lespedeza, tomatillo, trefoil	**Cancelled**	
6/2006 IRED	Cherries (SLN), citrus, pears	Maximum 1 lb ai/A per application	
		Maximum 1 application per year	
	Cherries	Maximum 0.33 lb ai/A per application	
		Maximum 2 applications per year	
		14 days application interval	
	Asparagus	Maximum 0.5 lb ai/A per application	
		Maximum 1 application per year	
	Alfalfa (seed and hay) field corn, popcorn, safflower, wheat	Maximum 0.5 lb ai/A per application	
		Maximum 1 application per year	
	Succulent peas	Maximum 0.16 lb ai/A per application	
		Maximum 1 application per year	

Decision Document	Use Site	Mitigation	Residential Uses Remaining
	Fresh beans, snap beans, lima beans, dry beans, cotton	Maximum 0.5 lb ai/A per application	
		Maximum 2 applications per year	
		14 day application interval	
	Broccoli, cauliflower, Celery, Brussels sprouts	Maximum 0.5 lb ai/A per application	
		Maximum 3 applications per year	
		7 day application interval	
	Lentils, melon, potatoes, soybeans, sorghum	Maximum 0.5 lb ai/A per application	
		Maximum 2 applications per year	
		7 day application interval	
	Tomatoes	Maximum 0.5 lb ai/A per application	
		Maximum 2 applications per year	
		6 day application interval	
	Pecans, peppers	Maximum 0.33 lb ai/A per application	
		Maximum 3 applications per year	
		7 day application interval	
	Grass for seed	Maximum 0.5 lb ai/A per application	
		Maximum 2 applications per year	
		90 day application interval	
	Leaf lettuce, Swiss chard, Endive (escarole), turnips	Maximum 0.25 lb ai/A per application	
		Maximum 3 applications per year	
		7 day application interval	

Decision Document	Use Site	Mitigation	Residential Uses Remaining
	Kale	Maximum 0.25 lb ai/A per application	
		Maximum 2 applications per year	
		15 day application interval	
	Mustard greens	Maximum 0.25 lb ai/A per application	
		Maximum 2 applications per year	
		9 day application interval	
	Herbaceous ornamentals	Maximum 0.25 lb ai/A per application	
		Maximum 1 application per year	
	Douglas fir seed orchards in Washington and Oregon	Maximum 4.15 lb ai/A per application	
		Maximum 1 application per year	
	Conifer seed orchards	Maximum 1.0 lb ai/A per application	
		Maximum 1 application per year	
	Woody ornamentals and Christmas tree nurseries	Maximum 1.0 lb ai/A per application	
		Maximum 3 applications per year	
		14 day application interval	

Decision Document	Use Site	Mitigation	Residential Uses Remaining
DDVP			
6/2006 IRED	Cucumbers, lettuce, radishes, tomatoes, edible swine tissue	**Cancelled**	**Remaining Uses:** 16 gram pest strip 5.25 gram pest strip 10.5 gram pest strip Pet collars Indoor aerosol spray **The following are restricted to use only in unoccupied areas and dwellings that remain unoccupied for more than four months:** 65g pest strip 80g pest strip
	100 gram pest strip	**Cancelled**	
	21 gram pest strip		
	Total release fogger	**Cancelled**	
	Lawn, turf, ornamentals, crack, crevice	**Cancelled**	
	Mushroom house hand held fogger, Greenhouse hand held fogger, Warehouse hand held fogger	**Cancelled**	
DIOXATHION-All Uses Cancelled			
DISULFOTON			
3/2002 IRED	Barley, berries, corn, oats, pecans, potatoes, tomatoes, triticale, wheat	**Cancelled**	End use products containing less than 2% active ingredient (for use on ornamentals only)
	Home vegetable gardens	**Cancelled**	
	Most residential products	**Cancelled all residential products except those for use on ornamentals containing less than 2% active ingredient**	
	Cotton	No aerial application	

Decision Document	Use Site	Mitigation	Residential Uses Remaining
	EUP for Cotton Seed Treatment	**Cancelled**	
	Impregnated fertilizer spikes	**Cancelled**	
	Asparagus	Maximum 2 applications per year	
	Snap beans, lima beans	Maximum rate 1 lb ai/A	
	Cabbage	Prohibit chemigation application methods	
	Cole Crops, lettuce, peppers	Use in California only	
	Broccoli, cauliflower, peanuts,	Maximum 1 lb ai/A	
	Radishes grown for seed, clover grown for seed	Use in Washington only	
	Ornamentals (nurseries)	**Cancelled**	
	Christmas trees (limited to firs)	Maximum application rate 4.5 lb ai/A pear year	
ETHION-All Uses Cancelled			
ETHOPROP			
6/20002 IRED	Peanuts, snap beans, citrus seedlings, lima beans	**Cancelled**	None
	Golf course products	**Cancelled**	
ETHYL PARATHION-All Uses Cancelled			
FENAMIPHOS-All Uses Cancelled			

Decision Document	Use Site	Mitigation	Residential Uses Remaining
FENITROTHION-No Mitigation Necessary			
FENTHION-All Uses Cancelled			
FONOFOS-All Uses Cancelled			
FOSTHIAZATE-No Mitigation Necessary (New Active Ingredient)			
ISAZOPHOS-All Uses Cancelled			
ISOFENPHOS-All Uses Cancelled			
MALATHION			
7/2006 IRED	29 use sites	Rate Reductions	Homeowner fruit trees, homeowner ornamentals, homeowner vegetables/ small fruits, homeowner outdoor building perimeter treatments, outdoor yard
	70 use sites	Decreased the number of applications per year	
	Pet uses, indoor uses, greenhouse uses, broadcast turf	**Cancelled**	
	Pressurized can formulations, residential dust formulations	**Cancelled**	
METHAMIDOPHOS			
4/2002 IRED	Cotton	**Phased out by 2009**	None
METHIDATHION-No Relevant Mitigation Necessary			
METHYL PARATHION			

Decision Document	Use Site	Mitigation	Residential Uses Remaining
1999 Cancellation Order (64 FR 57877)	Apples, artichokes, broccoli, Brussels sprouts, carrots, cauliflower, celery, cherries, clover, collards, filberts, garden beets, grapes, kale, kohlrabi, lettuce, mustard greens, nectarines, peaches, pears, plums, rutabagas, sorghum, succulent beans, succulent peas, tomatoes, turnips, vetch	**Cancelled**	None
	Christmas trees, chrysanthemums, daisies, field grown ornamentals, flowering plants, forest, grasses grown for seed, guayule, jojoba, marigolds, any mosquito larvicide use, nursery stock, non-agricultural land, roadside areas, wasteland.	**Cancelled**	
3/2001 IRED	Cabbage, dried beans, dried peas, hops, lentils, pecans, sugar beets	**Cancelled**	
	Alfalfa	Maximum 1.0 lb ai/A per year	
		Maximum 6 application per year	
		PHI of 15 days	
	Almonds	Maximum 2.0 lb ai/A per year	
		Maximum 4 applications per year	
		PHI of 28 days	

Decision Document	Use Site	Mitigation	Residential Uses Remaining
	Barley, oats, rice, and wheat	Maximum 0.75 lbs ai/A per year	
		Maximum 2 applications per year	
		PHI of 14 days	
	Corn (emulsifiable concentrate)	Maximum 0.5 lb ai/A per year	
		Maximum 2 applications per year	
		PHI of 12 days	
	Corn (microencapsulated formulations)	Maximum 1 lb ai/A per year	
		Maximum 3 applications per year	
		PHI of 12 days	
	Sweet Corn (emulsifiable concentrate formulations)	Maximum 0.5 lb ai/A per year	
		Maximum 2 applications per year	
		PHI of 12 days	
	Sweet corn (microencapsulated formulations)	Maximum 0.75 lb ai/A per year	
		Maximum 4 applications per year	
		PHI of 12 days	

Decision Document	Use Site	Mitigation	Residential Uses Remaining
	Cotton (emulsifiable concentrate formulations)	Maximum 0.75 lb ai/A per year	
		Maximum 5 applications per year	
		PHI of 7 days	
	Cotton (microencapsulated formulations)	Maximum 1.0 lb ai/A per year	
		Maximum 4 applications per year	
		PHI of 14 days	
	Grasses grown for forage, fodder, hay, range) (emulsifiable concentrate formulations)	Maximum 0.75 lb ai/A per year	
		Maximum 4 applications per year	
		PHI of 15 days	
	Onions (emulsifiable concentrate formulations)	Maximum 0.5 lb ai/A per year	
		Maximum 2 applications per year	
		PHI of 15 days	
	Onions (microencapsulated formulations)	Maximum 0.5 lb ai/a per year	
		Maximum 4 applications per year	
		PHI of 15 days	
	Rapeseed (canola)- emulsifiable concentrate formulations	Maximum 0.5 lb ai/A per year	
		Maximum 2 applications per year	
		PHI of 28 days	
	Rye (emulsifiable concentrate formulations)	Maximum 0.75 lb ai/A per year	
		Maximum 2 applications per year	

Decision Document	Use Site	Mitigation	Residential Uses Remaining
		PHI of 15 days	
	Soybeans (emulsifiable concentrate formulations)	Maximum 0.5 lb ai/A per year	
		Maximum 2 applications per year	
		PHI of 30 days	
	Soybeans (microencapsulated formulations)	Maximum 0.75 lb ai/A per year	
		Maximum 2 applications per year	
		PHI of 30 days	
	Sunflower (emulsifiable concentrate formulations)	Maximum 1.0 lb ai/A per year	
		Maximum 2 applications per year	
		PHI of 30 days	
	Sweet potatoes and yams (microencapsulated formulations)	Maximum 0.75 lb ai/A per year	
		Maximum 8 applications per year	
		PHI of 5 days	
	Walnuts (microencapsulated formulations)	Maximum 2.0 lb ai/A per year	
		Maximum 4 applications per year	
		PHI of 14 days	
	White potatoes (emulsifiable concentrate formulations)	Maximum 0.75 lb ai/A per year	

Decision Document	Use Site	Mitigation	Residential Uses Remaining
		Maximum 3 applications per year	
		PHI 5 days	
	White potatoes (microencapsulated formulations)	Maximum 1.5 l ai/A per year	
		Maximum 4 applications per year	
		PHI of 5 days	
MEVINPHOS-All Uses Cancelled			
MONOCROTOPHOS-All Uses Cancelled			
NALED			
1/2002 IRED	None	None	Black fly control, wide and general outdoor treatment of mosquitoes
OXYDEMETON- METHYL (ODM)			
8/2002 IRED	Field corn, pears, popcorn, snap beans, turnips	**Cancelled**	None
	Eggplants, bell peppers	**Cancelled (but tolerances will be retained for imports)**	
	Special Local Need use for Seed orchard trees in MT	**Cancelled**	
	Ornamentals in interior plant-scapes, ornamental gardens, parks, golf courses, lawns, grounds	**Cancelled**	

Decision Document	Use Site	Mitigation	Residential Uses Remaining
	Alfalfa grown for seed	PHI of 21 days	
	Lima beans	Maximum 2 applications per crop cycle	
		PHI of 21 days	
	Sugar beets	Maximum 0.5 lb ai per crop cycle	
		Maximum 1 application per crop cycle	
		PHI of 30 days	
	Broccoli, broccoli raab, cauliflower	Maximum 2 applications per crop cycle	
		PHI of 7 days	
	Brussels sprouts	PHI of 10 days	
	Cabbage	PHI of 7 days	
	Carrots grown for seed	PHI of 21 days	
	Citrus: Oranges, lemons, grapefruit	PHI of 7 days	
	Special Local Need in FL		
	Clover grown for seed	PHI of 21 days	
	Sweet corn	Use restricted to west of the Rockies	
		Maximum 2 applications per crop cycle	
		PHI of 26 days	
	Cotton	Maximum 0.5 lb ai/A	
		1 application per crop cycle	
		Use restricted to CA and AZ	
		PHI of 14 days	

Decision Document	Use Site	Mitigation	Residential Uses Remaining
	Cucurbits	Maximum 1 application per crop cycle	
		PHI of 14 days	
	Filberts	PHI of 116 days	
	Non-bearing fruit trees, apples, apricots, cherries, crab apples, nectarines, peaches, plums, prunes, quinces	Maximum 2 applications per crop cycle	
	Head lettuce	Maximum 2 applications per crop cycle	
		PHI of 21-28 days	
	Mint	PHI of 14 days	
	Spanish bulb onions	Maximum 0.5 lb/A	
		Maximum 2 applications per crop cycle	
		PHI of 30 days	
	Safflower	Maximum 0.5 lb/ A	
		Maximum 2 applications per crop cycle	
		PHI of 7 days	
	Sorghum	Maximum 2 applications per crop cycle	
		PHI of 45 day for grain sorghum	

Decision Document	Use Site	Mitigation	Residential Uses Remaining
		PHI of 21 days for grazing sorghum	
	Strawberries (OR and WA special local need)	Maximum 2 application per crop cycle	
		No application to fruit	
	Walnuts	PHI of 30 days	
PHORATE			
3/2001 IRED	Wheat, peanuts	Prohibit use at pegging	None
PHOSALONE-No Mitigation necessary			
PHOSMET			
10/2001 IRED	Kiwifruit	PHI of 28 days	None
	Green Peas	PHI of 18 days	
	Lowbush blueberries	PHI of 7 days	
	Sweet cherries	Maximum 5.25 lb ai/A per year	
		PHI of 19 days	
	Tart cherries	Maximum 5.25 lb ai/A per year	
	Pears	Maximum application 4.0 lb ai/A	
		Maximum 11.2 lb ai/A pear year	
	Grapes: 1.0 lb ai/A application rate	Maximum 4.55 lb ai/A per year	
	Pistachios	Maximum 12 lb ai/A per year	

Decision Document	Use Site	Mitigation	Residential Uses Remaining
	Pecans	Maximum 7 lb ai/A per year	
	Walnuts	Maximum 12 lb ai/A per year	
	Filberts, brazil nuts, beechnuts, butternuts, cashew, chestnut, chinquapin, hickory nuts, macadamia nuts	Maximum 12 lb ai/A per year	
		PHI of 28 days	
	Residential uses- domestic pets, household ornamentals, household fruit trees	**Cancelled**	
PHOSPHAMIDON-All Uses Cancelled			
PHOSTEBUPIRIM-No Relevant Mitigation Necessary			
PRIMIPHOS METHYL-No Relevant Mitigation necessary			
PROFENOFOS-No Relevant Mitigation Necessary			
PROPETAMPHOS-No Relevant Mitigation Necessary			
SULFOTEPP-All Uses Cancelled			
SULPROFOS-All Uses Cancelled			
TEMEPHOS-No Relevant Mitigation Necessary (Mosquito larvicide use only)			
TERBUFOS			
9/2001 IRED	Sorghum	Maximum 1.70 lb ai/A	None
TETRACHLORVINPHOS			

Decision Document	Use Site	Mitigation	Residential Uses Remaining
12/2002 IRED			Cats, dogs, domestic indoor premises, spot treatments
TRIBUFOS			
12/2000 IRED	Cotton	1.125 lb ai/A in all states except California and Arizona	
TRICHLORFON			
9/2001 IRED	Ant mounds, house perimeter	**Cancelled**	Home lawns
	Golf courses	Maximum 3 applications per calendar year	
		Use on fairways limited to spot treatment	
	Golf courses- Broadcast and chemigation formulations	Limit to tees and greens	

B-1. Benchmark dose calculations for selected OPs from repeated dosing comparative ChE studies

Table II.B-1.1 Summary Table BMD Runs for Repeated Dosing from Comparative Cholinesterase Studies for Select OPs.

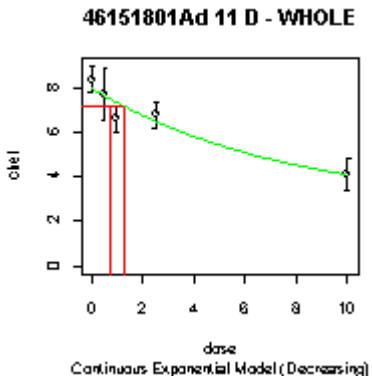
OP	Gender	Age	BMD	BMDL	P Value
Acephate	Male	Adult	0.274	0.224	0.023
		Pup	0.417	0.303	0.469
	Female	Adult	1.245	0.732	0.099
		Pup	1.127	0.597	0.59
Azinphos	Female	Adult	1.14	1.04	N/A
		Pup	0.25	0.22	
Diazinon	Male	Adult	40.57	27.87	0.537
		Pup	1.075	0.998	1.35E-06
	Female	Adult	0.385	0.29	0.646
		Pup	0.723	0.676	0.008
Disulfoton	Male	Adult	0.107	0.089	0.109
		Pup	0.048	0.045	0.021
	Female	Adult	0.066	0.055	0.044
		Pup	0.045	0.043	0.055
Dicrotophos	Male	Adult	0.109	0.085	0.228
		Pup	0.064	0.051	0.466
	Female	Adult	0.0867	0.0716	0.0198
		Pup	0.05	0.044	0.786
DDVP (Concurrent controls)	Male	Adult	0.72	0.55	0.71
		Pup	0.88	0.75	0.0081
	Female	Adult	0.88	0.71	0.84
		Pup	0.95	0.8	0.022
DDVP (Historical controls)	Male	Adult	0.77	0.62	0.63
		Pup	0.84	0.65	0.37
	Female	Adult	0.92	0.75	0.75
		Pup	0.85	0.62	0.39
Dimethoate	Male	Adult	0.484	0.218	0.866
		Pup	0.392	0.289	0.588
	Female	Adult	0.366	0.338	0.7
		Pup	0.408	0.261	0.812
Fosthiazate	Male	Adult	1.886	1.651	0.161

OP	Gender	Age	BMD	BMDL	P Value
		Pup	0.737	0.588	0.899
	Female	Adult	0.597	0.552	0.137
		Pup	0.477	0.436	0.278
Methamidophos	Male	Adult	0.103	0.083	0.112
		Pup	0.076	0.0605	0.552
	Female	Adult	0.181	0.112	0.091
		Pup	0.091	0.083	0.964
Methyl Parathion	Male	Adult	Poor fit		
		Pup	0.086	0.073	0.148
	Female	Adult	0.658	0.503	0.0002
		Pup	0.106	0.094	0.811
Phorate	Male	Pup	0.044	0.031	0.975
	Female	Pup	4015	0.07	1
Terbufos	Male	Adult	0.098	0.043	0.428
		Pup	0.015	0.013	0.573
	Female	Adult	0.015	0.008	0.562
		Pup	0.016	0.013	0.181

1. Acephate

a. Adult, Repeated

```
                    Acephate:11-D:BRAIN:F:WHOLE
                       Sun  Feb 17 20:03:43 2002
                MRID: 46151801Ad   Guideline: NONGUIDELINE
                Continuous Exponential Model (Decreasing)
                Formula: chei = B + (A-B)*exp(-(m*dose)^g)

Variance Function: power


   The BMD corresponds to a dose that results in a 10% reduction in the
                    response relative to the control
    ------------------------------------------------------------------
                    Summary of Model Fitting Results

      AIC       BIC    logLik
161.51294 169.16103 -76.75647

Coefficients:
     Value Std.Error
A 8.011424 0.3448424
B 2.646285 2.2022807
m 0.129940 0.1094992

Correlation:
          A         B         m
A 1.0000000 0.6331860 0.6896269
B 0.6331860 1.0000000 0.9880074
m 0.6896269 0.9880074 1.0000000

Approximate 95% confidence intervals

 Coefficients:
       lower     est.      upper
A 7.34687854 8.011424  8.7360802
B 0.49606624 2.646285 14.1167128
m 0.02385034 0.129940  0.7079315

 Residual standard error:
   lower     est.    upper
1.236741 1.485630 1.860871

Degrees of freedom: 50 total; 47 residual
    ------------------------------------------------------------------
                            Goodness of Fit
 The chi-squared goodness-of-fit values should be taken as general
indications of fit only.  P-values are likely to be inaccurate to some
degree
```



Pearson Chi-Square Statistic: 4.627 with 2 degrees of freedom. P = 0.099

	dose	n	chei	Expected	sd	Exp.SD	X2 Resid.
1	0.0	10	8.41	8.011424	0.81	1.428793	0.88214790
2	0.5	10	7.72	7.673933	1.66	1.359658	0.10714137
3	1.0	10	6.63	7.357672	0.83	1.296091	-1.77541618
4	2.5	10	6.82	6.523326	0.86	1.134498	0.82694221
5	10.0	10	4.10	4.109334	1.01	0.730546	-0.04040200

BMD Computation

BMD = 1.245: BMDL = 0.7322

Potency Measures

A unit dose (1 mg/kg) would result in 100*exp(-Potency)% of background activity

Potency: 0.1299
se: 0.1095
var=se^2: 0.01199
Per cent. of background at unit dose: 88
Per cent. of background at the highest dose: 27
ED50 (95% CI): 5.334 (1.023 , 27.82)

ln(Potency) -2.041
se[log(Potency)]: 0.8427
se[log(Potency)]^2: 0.7101

Acephate:11-D:BRAIN:M:WHOLE
Sun Feb 17 20:05:10 2002
MRID: 46151801Ad Guideline: NONGUIDELINE
Continuous Exponential Model (Decreasing)
Formula: chei = B + (A-B)*exp(-(m*dose)^g)

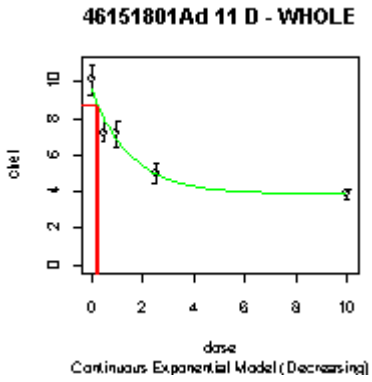
Variance Function: power

The BMD corresponds to a dose that results in a 10% reduction in the response relative to the control

---

Summary of Model Fitting Results

```
      AIC       BIC    logLik
131.89215 139.54024 -61.94608

Coefficients:
      Value  Std.Error
A 9.6420821 0.35366253
B 3.8842311 0.17198632
m 0.6679441 0.08848987

Correlation:
          A         B         m
A 1.0000000 0.1215402 0.6056173
B 0.1215402 1.0000000 0.5387317
m 0.6056173 0.5387317 1.0000000

Approximate 95% confidence intervals

 Coefficients:
      lower      est.     upper
A 8.9562204 9.6420821 10.380467
B 3.5532015 3.8842311  4.246101
m 0.5116738 0.6679441  0.871941

 Residual standard error:
   lower     est.    upper
1.144370 1.374670 1.721885

Degrees of freedom: 50 total; 47 residual
```



Goodness of Fit

The chi-squared goodness-of-fit values should be taken as general indications of fit only. P-values are likely to be inaccurate to some degree

Pearson Chi-Square Statistic: 7.592 with 2 degrees of freedom. P = 0.0225

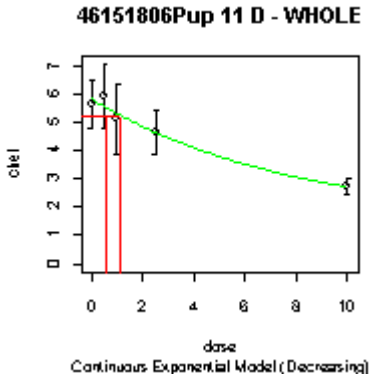
	dose	n	chei	Expected	sd	Exp.SD	X2 Resid.
1	0.0	10	10.11	9.642082	1.21	1.3353162	1.1081169
2	0.5	10	7.23	8.007277	0.64	1.0850213	-2.2653624
3	1.0	10	7.15	6.836636	0.97	0.9136781	1.0845647
4	2.5	10	5.01	4.968281	0.82	0.6611181	0.1995515
5	10.0	10	3.87	3.891466	0.40	0.5422303	-0.1251876

```
------------------------------------------------------------------
                        BMD Computation

                  BMD = 0.2744:  BMDL = 0.2239

------------------------------------------------------------------
                        Potency Measures

A unit dose (1 mg/kg) would result in 100*exp(-Potency)% of background
activity

Potency: 0.6679
se: 0.08849
var=se^2: 0.00783
Per cent. of background at unit dose: 51
Per cent. of background at the highest dose: 0.13
ED50 (95% CI): 1.038 ( 0.8004 , 1.345 )

ln(Potency) -0.4036
se[log(Potency)]: 0.1325
```

se[log(Potency)]^2: 0.01755

b. Pup, Repeated

```
                    Acephate:11-D:BRAIN:F:WHOLE
                      Sun Feb 17 20:07:16 2002
               MRID: 46151806Pup   Guideline: NONGUIDELINE
                Continuous Exponential Model (Decreasing)
                Formula: chei = B + (A-B)*exp(-(m*dose)^g)

Variance Function: power


   The BMD corresponds to a dose that results in a 10% reduction in the
                    response relative to the control
    ------------------------------------------------------------------
                    Summary of Model Fitting Results

      AIC       BIC    logLik
160.85705 168.50514 -76.42852

Coefficients:
      Value Std.Error
A 5.8213724 0.3485573
B 1.5350994 2.2279159
m 0.1294797 0.1387498

Correlation:
          A         B         m
A 1.0000000 0.6381198 0.6904093
B 0.6381198 1.0000000 0.9898527
m 0.6904093 0.9898527 1.0000000

Approximate 95% confidence intervals

 Coefficients:
       lower      est.     upper
A 5.16075137 5.8213724  6.566559
B 0.08282063 1.5350994 28.453420
m 0.01499557 0.1294797  1.117997

 Residual standard error:
   lower     est.    upper
1.222280 1.468260 1.839113

Degrees of freedom: 50 total; 47 residual
    ------------------------------------------------------------------
                              Goodness of Fit
 The chi-squared goodness-of-fit values should be taken as general
indications of fit only.  P-values are likely to be inaccurate to some
degree

Pearson Chi-Square Statistic: 1.057 with 2 degrees of freedom.  P =
0.59
```



	dose	n	chei	Expected	sd	Exp.SD	X2 Resid.
1	0.0	10	5.63	5.821372	1.21	1.4418224	-0.419727664
2	0.5	10	5.92	5.552671	1.63	1.3765497	0.843845474
3	1.0	10	5.13	5.300815	1.74	1.3152118	-0.410704778
4	2.5	10	4.63	4.636080	1.11	1.1525052	-0.016681218
5	10.0	10	2.71	2.709338	0.38	0.6712756	0.003117330

BMD Computation

BMD = 1.127: BMDL = 0.5966

Potency Measures

A unit dose (1 mg/kg) would result in 100*exp(-Potency)% of background activity

Potency: 0.1295
se: 0.1387
var=se^2: 0.01925
Per cent. of background at unit dose: 88
Per cent. of background at the highest dose: 27
ED50 (95% CI): 5.353 (0.6553 , 43.73)

ln(Potency) -2.044
se[log(Potency)]: 1.072
se[log(Potency)]^2: 1.148

Acephate:11-D:BRAIN:M:WHOLE
Sun Feb 17 20:07:46 2002
MRID: 46151806Pup Guideline: NONGUIDELINE
Continuous Exponential Model (Decreasing)
Formula: chei = B + (A-B)*exp(-(m*dose)^g)

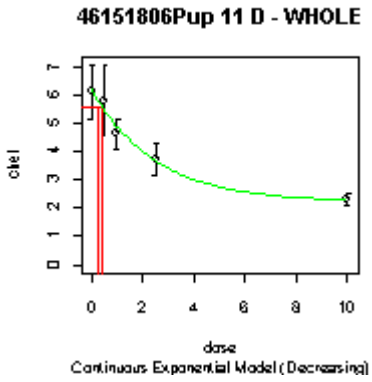
Variance Function: power

The BMD corresponds to a dose that results in a 10% reduction in the response relative to the control

---

Summary of Model Fitting Results

```
      AIC       BIC    logLik
138.52646 146.17455 -65.26323

Coefficients:
      Value Std.Error
A 6.2327529 0.3367764
B 2.2232011 0.1901778
m 0.4053003 0.0940682

Correlation:
          A         B         m
A 1.0000000 0.2302019 0.6474848
B 0.2302019 1.0000000 0.6063487
m 0.6474848 0.6063487 1.0000000

Approximate 95% confidence intervals

 Coefficients:
      lower      est.     upper
A 5.5907703 6.2327529 6.9484537
B 1.8717224 2.2232011 2.6406816
m 0.2540963 0.4053003 0.6464807

 Residual standard error:
   lower     est.    upper
1.102686 1.324597 1.659164

Degrees of freedom: 50 total; 47 residual
```



Goodness of Fit

The chi-squared goodness-of-fit values should be taken as general indications of fit only. P-values are likely to be inaccurate to some degree

Pearson Chi-Square Statistic: 1.516 with 2 degrees of freedom. P = 0.469

	dose	n	chei	Expected	sd	Exp.SD	X2 Resid.
1	0.0	10	6.14	6.232753	1.35	1.3462446	-0.21787306
2	0.5	10	5.82	5.497256	1.75	1.1862684	0.86034964
3	1.0	10	4.62	4.896676	0.79	1.0558512	-0.82864583
4	2.5	10	3.73	3.678816	0.77	0.7921963	0.20431435
5	10.0	10	2.29	2.292847	0.30	0.4949919	-0.01819131

```
------------------------------------------------------------------
                        BMD Computation

                BMD = 0.4168:   BMDL = 0.3031

------------------------------------------------------------------
                        Potency Measures

A unit dose (1 mg/kg) would result in 100*exp(-Potency)% of background
activity

Potency: 0.4053
se: 0.09407
var=se^2: 0.008849
Per cent. of background at unit dose: 67
Per cent. of background at the highest dose: 1.7
ED50 (95% CI): 1.71 ( 1.085 , 2.695 )

ln(Potency) -0.9031
se[log(Potency)]: 0.2321
```

se[log(Potency)]^2: 0.0538

2. Azinphos

a. Adult and Pup Repeated

Dose Response Modeling of Rat Brain AChE Activity: AZM in Adult and PND 11 Females

March 31, 2006

1 Preamble

Here is some code to set up the analysis: loading required libraries and datasets, and defining some functions.
Load the library DRUtils.

```
> library(DRUtils)
```

Set up lattice to use B&W instead of color:

```
> library(lattice)
> ltheme <- canonical.theme(color = FALSE)
> ltheme$strip.background$col <- "transparent"
> lattice.options(default.theme = ltheme)
```

Use package Hmisc for some formatting support.

```
> library(Hmisc)
```

The following function turns out to be quite useful on subsetted dataframes. It just eliminates unused levels of all factors in the data frame:

```
> CleanUp <- function(x) {
+     for (nm in names(x)) {
+         if (is.factor(x[, nm]))
+             x[, nm] <- factor(x[, nm])
+     }
+     x
+ }
```

To get starting values, we often have to extract values from a previously fit model. The following function simplifies that. The argument what is a regular expression:

```
> getParms <- function(what, Par) {
+     Par[grep(what, names(Par))]
+ }
```

This script is for modeling the dose-time response for rat brain via gavage dosing in both adult and juvenile females, and estimating the ratio of potencies in the two age groups.
First, read in the data from local ".csv" files:

```
> adult <- subset(read.csv("Adults.csv"), sex == "F" & compartment ==
+     "BRAIN")
> pnd11 <- subset(read.csv("pnd11.csv"), sex == "F" & compartment ==
+     "BRAIN")
```

Summary of the relevant variables in these datasets:

```
> adult[, c("dose", "chei", "sd", "n")]

   dose chei  sd n
6  0.00 13.8 0.5 6
7  0.25 14.4 0.3 6
8  0.54 13.5 0.6 6
9  1.00 13.3 0.5 6
10 1.60  5.2 2.4 6

> pnd11[, c("dose", "chei", "sd", "n")]

  dose chei  sd  n
5 0.00 10.4 0.3 12
6 0.24  9.6 0.4 12
7 0.51  7.4 0.9 11
8 1.00  4.8 1.0 11
```

Use PhonyDF() to set up a pseudo-individual dataset.

```
> adult.w <- with(adult, PhonyDF(dose, n, chei, sd, "dose", "chei"))
> pnd11.w <- with(pnd11, PhonyDF(dose, n, chei, sd, "dose", "chei"))
```

The model that has been fit to the carbamate data is:

$$\mathrm{E}(y) = A(1 - g(d; R, P, D, \gamma))$$

where

$$g(d; R, P, D, \gamma) = (1 - P)(1 - e^{ln(\frac{1-R-P}{1-P})(\frac{d}{D})^{\gamma}})$$

and

$$\begin{aligned} A &= e^{lA} \\ R &= \text{constant}: 0.1 \\ D &= e^{lD} \\ P &= \frac{1-R}{1+exp(-tz)} \\ \gamma &= e^{l\gamma} \end{aligned}$$

This is captured in the following R function:

```
> drfn <- function(x, lA, lD, lg, tz, R = 0.1) {
+     A <- exp(lA)
+     .exprP3 <- exp(-tz)
+     .exprP4 <- 1 + .exprP3
+     P <- (1 - R)/.exprP4
+     D <- exp(lD)
+     g <- exp(lg)
+     .expr1 <- 1 - P
+     .expr3 <- 1 - R - P
+     .expr4 <- .expr3/.expr1
+     .expr5 <- log(.expr4)
+     .expr6 <- x/D
+     .expr7 <- .expr6^g
+     .expr9 <- exp(.expr5 * .expr7)
```

```
+     .expr10 <- 1 - .expr9
+     .expr12 <- 1 - .expr1 * .expr10
+     .value <- A * .expr12
+     .grad <- array(0, c(length(.value), 4), list(NULL, c("lA",
+         "tz", "lD", "lg")))
+     .grad[, "lA"] <- .expr12 * A
+     .grad[, "tz"] <- ifelse(x > 0, -(A * (.expr1 * (.expr9 *
+         ((1/.expr1 - .expr3/.expr1^2)/.expr4 * .expr7)) - .expr10)) *
+         P * .exprP3/.exprP4, 0)
+     .grad[, "lD"] <- ifelse(x > 0, -(A * (.expr1 * (.expr9 *
+         (.expr5 * (.expr6^(g - 1) * (g * (x/D^2)))))) * D, 0)
+     .grad[, "lg"] <- ifelse(x > 0, A * (.expr1 * (.expr9 * (.expr5 *
+         (.expr7 * log(.expr6))))) * g, 0)
+     attr(.value, "gradient") <- .grad
+     .value
+ }
```

2 Dose-Response Modeling

The parameters of this model will be estimated using generalized non-linear least squares. First, we get initial parameter estimates for the two datasets. Preliminary work shows that we cannot estimate tz with these data sets, so set that value to -10, and estimate the remaining parameters.

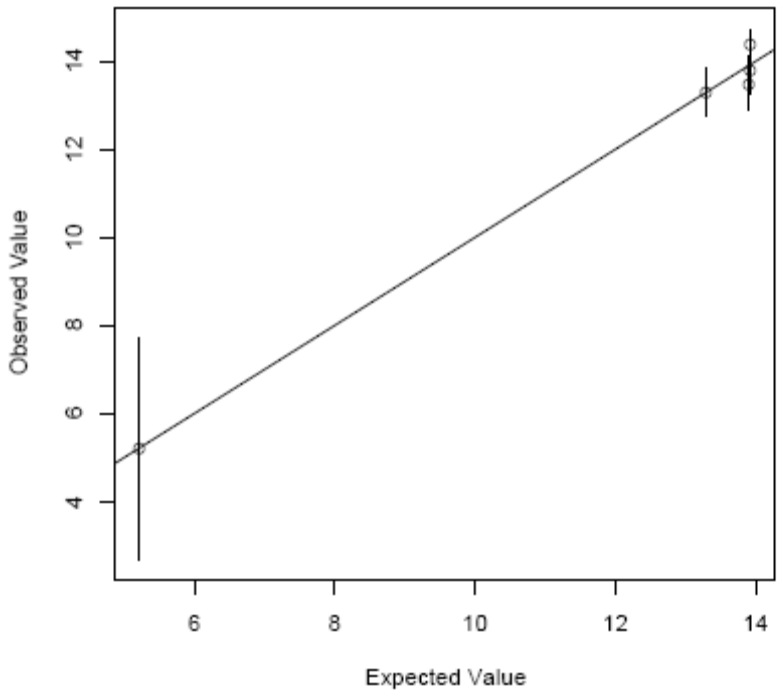
```
> formals(drfn)$tz <- -10
> if (!file.exists("Inits.RData")) {
+     adultinits <- GetInitialValues(chei ~ drfn(dose, lA, lD,
+         lg), data = adult.w, params = list(lA ~ 1, lD ~ 1, lg ~
+         1), start = c(log(10), log(1), 0), weights = varIdent())
+     pnd11inits <- GetInitialValues(chei ~ drfn(dose, lA, lD,
+         lg), data = pnd11.w, params = list(lA ~ 1, lD ~ 1, lg ~
+         1), start = c(log(10), log(1), 0), weights = varIdent())
+     save(adultinits, pnd11inits, file = "Inits.RData")
+ } else {
+     load("Inits.RData")
+ }
```

Now fit the models. Modeling the variance is a problem: in both datasets, the variance *increases* as the response *decreases*. In the adult dataset, the highest dose has a substantially greater variance than the lower doses, whose standard deviations all look pretty similar. We can accommodate that by creating a factor that identifies that high dose, and using a construction like varIdent(1|varfact).

```
> adult.w$varfact <- factor(adult.w$dose == max(adult.w$dose))
> out.adult <- gnls(chei ~ drfn(dose, lA, lD, lg), data = adult.w,
+     params = list(lA ~ 1, lD ~ 1, lg ~ 1), start = adultinits$start$beta,
+     weights = varIdent(form = ~1 | varfact))
> summary(out.adult)

Generalized nonlinear least squares fit
  Model: chei ~ drfn(dose, lA, lD, lg)
  Data: adult.w
       AIC      BIC    logLik
  75.71114 82.71712 -32.85557

Variance function:
 Structure: Different standard deviations per stratum
```

```
 Formula: ~1 | varfact
 Parameter estimates:
   FALSE     TRUE
1.000000 3.995321

Coefficients:
      Value  Std.Error   t-value p-value
lA 2.632562 0.00993628 264.94447  0.0000
lD 0.127092 0.05080395   2.50162  0.0187
lg 1.872529 0.15650512  11.96465  0.0000

 Correlation:
   lA     lD
lD -0.504
lg -0.452  0.854

Standardized residuals:
        Min          Q1         Med          Q3         Max
-2.11659541 -0.72701486  0.04170518  0.70602499  1.66422738

Residual standard error: 0.5780485
Degrees of freedom: 30 total; 27 residual
```

Plot of observed versus predicted values, with 95% confidence intervals for the observed values. If we fit the data, this should form a diagonal line along the $x = y$ line.



This results in an estimate of the standard deviation in the lower doses of

```
> out.adult$sigma

[1] 0.5780485
```

and in the high dose of

```
> out.adult$sigma * exp(coef(out.adult$modelStruct))

varStruct
 2.309489
```

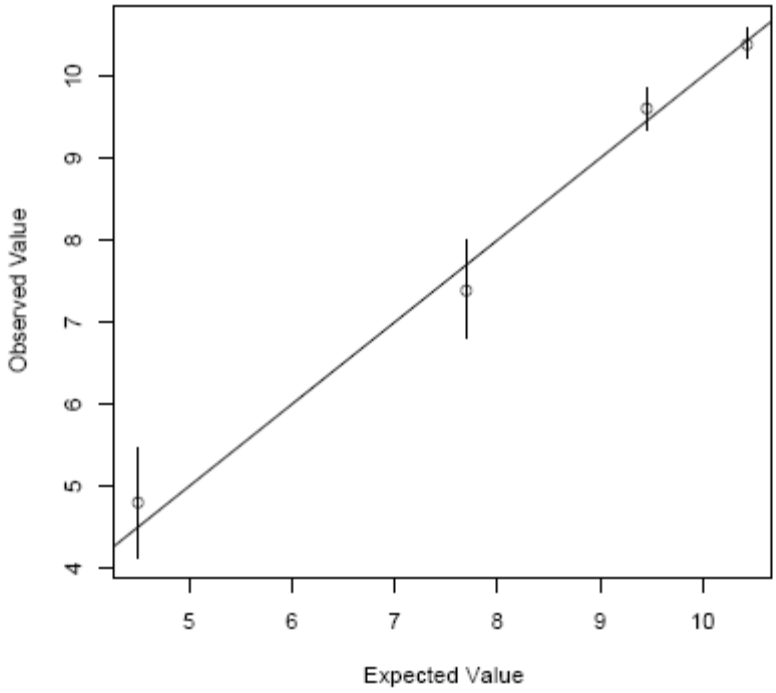
which compares favorably with the data.

In the PND11 dataset, the activity decreases more gradually with dose, while the standard deviation increases. Create a variable that is dose + 1, and try to fit a power model based on dose:

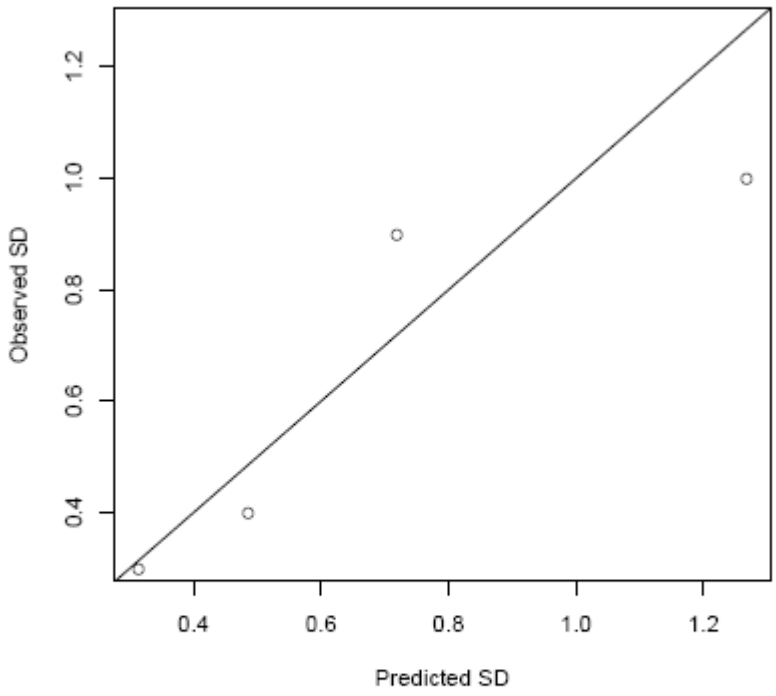
```
> pnd11.w$varval <- pnd11.w$dose + 1
> out.pnd11 <- gnls(chei ~ drfn(dose, lA, lD, lg), data = pnd11.w,
+     params = list(lA ~ 1, lD ~ 1, lg ~ 1), start = pnd11inits$start$beta,
+     weights = varPower(form = ~varval))
> summary(out.pnd11)
```

```
Generalized nonlinear least squares fit
  Model: chei ~ drfn(dose, lA, lD, lg)
  Data: pnd11.w
       AIC      BIC    logLik
  90.16405 99.30726 -40.08203

Variance function:
 Structure: Power of variance covariate
 Formula: ~varval
 Parameter estimates:
   power
2.012426

Coefficients:
        Value  Std.Error   t-value p-value
lA  2.3441899 0.00859987 272.58421       0
lD -1.3763981 0.09356099 -14.71124       0
lg  0.4104569 0.08879270   4.62264       0

 Correlation:
   lA     lD
lD -0.520
lg -0.376  0.873

Standardized residuals:
        Min          Q1         Med          Q3         Max
-2.39204717 -0.61400771  0.01437606  0.66349105  1.88194994

Residual standard error: 0.3138989
Degrees of freedom: 46 total; 43 residual
```

Again, plots of observed versus predicted:

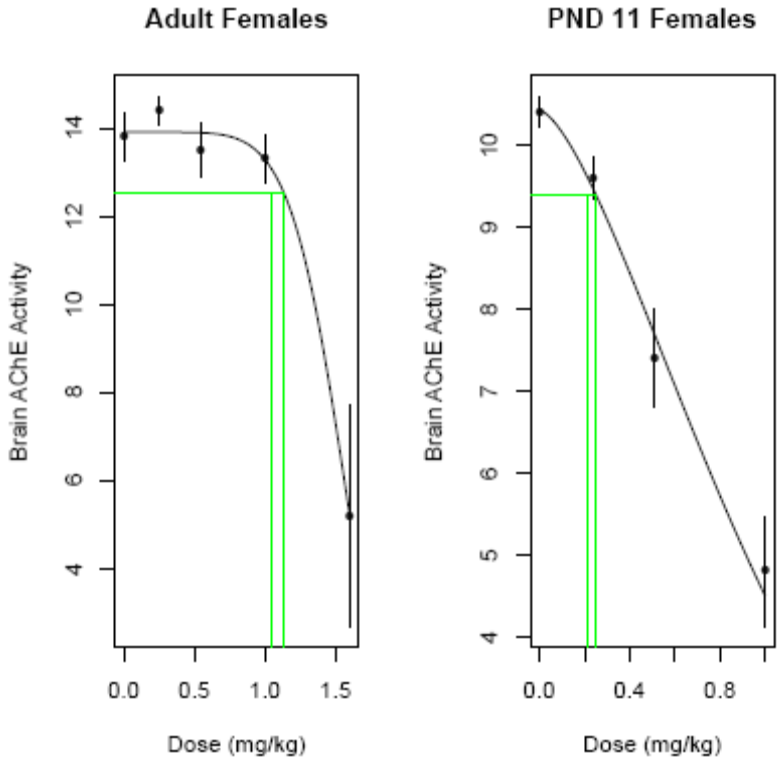


How well have we modeled the variance? Extract the standard deviations from the residual vector, and plot the observed standard deviations against them:



Again, the variance seems to be adequately modeled.

Finally, dose-response plots for both data sets (in the manner of BMDS):



3 Results

BMDs and BMDLs for adults and PND 11 females:

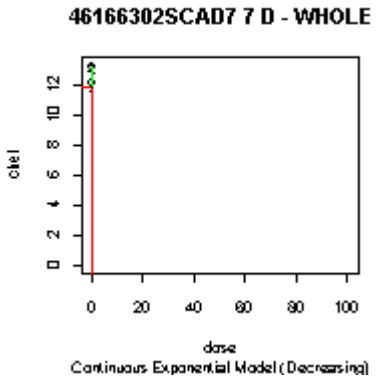
Age	BMD	BMDL	SE for ID
Adult	1.14	1.04	0.0508
PND 11	0.252	0.216	0.0936

This gives a relative potency between adults and pnd 11 pups of 4.5, with 95% confidence limits of (3.65, 5.54).

3. Diazinon

a. Adult, Repeated

```
                    DIAZINON:7-D:BRAIN:F:WHOLE
                      Fri Jan 04 17:11:44 1980
            MRID: 46166302SCAD7   Guideline: NONGUIDELINE
              Continuous Exponential Model (Decreasing)
              Formula: chei = B + (A-B)*exp(-(m*dose)^g)

Variance Function: power

Highest 2 doses dropped from data set.


   The BMD corresponds to a dose that results in a 10% reduction in the
                    response relative to the control
    ------------------------------------------------------------------
                    Summary of Model Fitting Results

      AIC       BIC    logLik
 35.04058  38.57474 -14.52029

Coefficients:
      Value  Std.Error
A 13.251126 0.12562346
m  0.273804 0.05446239

Correlation:
          A         m
A 1.0000000 0.6319335
m 0.6319335 1.0000000

Approximate 95% confidence intervals

 Coefficients:
       lower      est.      upper
A 12.9931429 13.251126 13.5142307
m  0.1812538  0.273804  0.4136114

 Residual standard error:
    lower      est.     upper
0.3674626 0.4751294 0.6724751

Degrees of freedom: 24 total; 22 residual
    ------------------------------------------------------------------
                              Goodness of Fit
 The chi-squared goodness-of-fit values should be taken as general
indications of fit only.  P-values are likely to be inaccurate to some
degree

Pearson Chi-Square Statistic: 0.2108 with 1 degrees of freedom.  P =
0.646

  dose n chei Expected  sd    Exp.SD   X2 Resid.
1 0.00 8 13.2 13.25113 0.3 0.4769697 -0.30317490
```



```
2 0.03 8 13.2 13.14273 0.2 0.4730678  0.34244076
3 0.30 8 12.2 12.20617 0.7 0.4393567 -0.03970068

    ------------------------------------------------------------------
                            BMD Computation

                      BMD = 0.3848:  BMDL = 0.2899

    ------------------------------------------------------------------
                            Potency Measures

A unit dose (1 mg/kg) would result in 100*exp(-Potency)% of background
activity

Potency: 0.2738
se: 0.05446
var=se^2: 0.002966
Per cent. of background at unit dose: 76
Per cent. of background at the highest dose: 92
ED50 (95% CI): 2.532 ( 1.714 , 3.739 )

ln(Potency) -1.295
se[log(Potency)]: 0.1989
se[log(Potency)]^2: 0.03957
```

DIAZINON:7-D:BRAIN:M:WHOLE
Fri Jan 04 17:11:50 1980
MRID: 46166302SCAD7 Guideline: NONGUIDELINE
Continuous Exponential Model (Decreasing)
Formula: chei = B + (A-B)*exp(-(m*dose)^g)

Variance Function: power

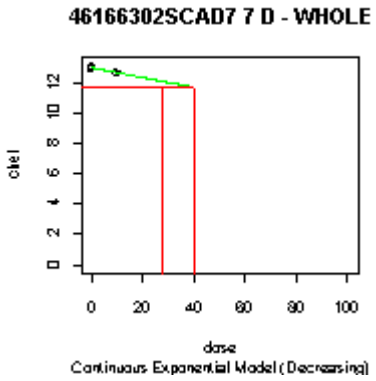
Highest 1 doses dropped from data set.

The BMD corresponds to a dose that results in a 10% reduction in the response relative to the control

---

Summary of Model Fitting Results

```
       AIC        BIC     logLik
-0.5037806  3.8934271  3.2518903

Coefficients:
         Value    Std.Error
A 13.036335314 0.0469126357
m  0.002596825 0.0007193943

Correlation:
          A         m
A 1.0000000 0.5162654
m 0.5162654 1.0000000

Approximate 95% confidence intervals

 Coefficients:
         lower         est.        upper
A 12.940878133 13.036335314 13.132496625
m  0.001474799  0.002596825  0.004572486

 Residual standard error:
    lower      est.     upper
0.1825069 0.2283872 0.3052791

Degrees of freedom: 32 total; 30 residual
```



Goodness of Fit

The chi-squared goodness-of-fit values should be taken as general indications of fit only. P-values are likely to be inaccurate to some degree

Pearson Chi-Square Statistic: 1.244 with 2 degrees of freedom. P = 0.537

	dose	n	chei	Expected	sd	Exp.SD	X2 Resid.
1	0.00	8	13.0	13.03634	0.3	0.2272773	-0.45218682
2	0.03	8	13.0	13.03532	0.2	0.2272596	-0.43958268
3	0.30	8	13.1	13.02618	0.2	0.2271003	0.91935170
4	10.00	8	12.7	12.70216	0.2	0.2214513	-0.02761669

BMD Computation

BMD = 40.57: BMDL = 27.87

Potency Measures

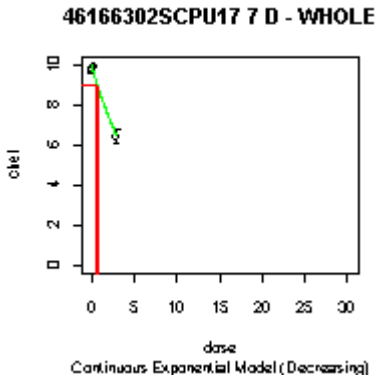
A unit dose (1 mg/kg) would result in 100*exp(-Potency)% of background activity

Potency: 0.002597
se: 0.0007194
var=se^2: 5.175e-07
Per cent. of background at unit dose: 100
Per cent. of background at the highest dose: 97
ED50 (95% CI): 266.9 (155.1 , 459.4)

ln(Potency) -5.953
se[log(Potency)]: 0.277
se[log(Potency)]^2: 0.07674

b. Pup, Repeated

```
                    DIAZINON:7-D:BRAIN:F:WHOLE
                      Fri Jan 04 17:12:04 1980
              MRID: 46166302SCPU17   Guideline: NONGUIDELINE
                Continuous Exponential Model (Decreasing)
                Formula: chei = B + (A-B)*exp(-(m*dose)^g)

Variance Function: power

Highest 1 doses dropped from data set.


   The BMD corresponds to a dose that results in a 10% reduction in the
                    response relative to the control
    ------------------------------------------------------------------
                    Summary of Model Fitting Results

      AIC       BIC    logLik
 48.72852  53.79516 -21.36426

Coefficients:
      Value  Std.Error
A 9.9492415 0.09056042
m 0.1458177 0.00606255

Correlation:
         A        m
A 1.000000 0.550473
m 0.550473 1.000000

Approximate 95% confidence intervals

 Coefficients:
      lower      est.     upper
A 9.7675903 9.9492415 10.134271
m 0.1340470 0.1458177  0.158622

 Residual standard error:
    lower      est.     upper
0.3886845 0.4756029 0.6129466

Degrees of freedom: 40 total; 38 residual
    ------------------------------------------------------------------
                              Goodness of Fit
 The chi-squared goodness-of-fit values should be taken as general
indications of fit only.  P-values are likely to be inaccurate to some
degree

Pearson Chi-Square Statistic: 9.696 with 2 degrees of freedom.  P =
0.00784


  dose  n chei Expected  sd    Exp.SD  X2 Resid.
```



```
1 0.00 10  9.8 9.949242 0.2 0.4774077 -0.9885538
2 0.03 10  9.7 9.905813 0.2 0.4753511 -1.3691751
3 0.30 10  9.9 9.523391 0.2 0.4572359  2.6046545
4 3.00 10  6.4 6.424014 0.5 0.3100258 -0.2449468

    ------------------------------------------------------------------
                            BMD Computation

                      BMD = 0.7225:  BMDL = 0.6763

    ------------------------------------------------------------------
                            Potency Measures

A unit dose (1 mg/kg) would result in 100*exp(-Potency)% of background
activity

Potency: 0.1458
se: 0.006063
var=se^2: 3.675e-05
Per cent. of background at unit dose: 86
Per cent. of background at the highest dose: 65
ED50 (95% CI): 4.754 ( 4.382 , 5.157 )

ln(Potency) -1.925
se[log(Potency)]: 0.04158
se[log(Potency)]^2: 0.001729
```

DIAZINON:7-D:BRAIN:M:WHOLE
Fri Jan 04 17:12:17 1980
MRID: 46166302SCPU17 Guideline: NONGUIDELINE
Continuous Exponential Model (Decreasing)
Formula: chei = B + (A-B)*exp(-(m*dose)^g)

Variance Function: power

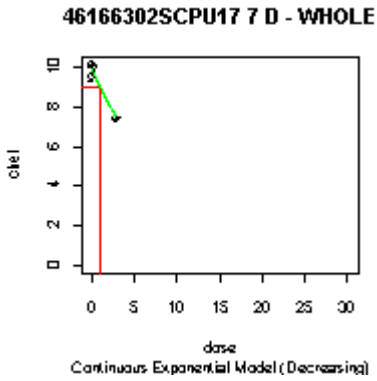
Highest 1 doses dropped from data set.

The BMD corresponds to a dose that results in a 10% reduction in the response relative to the control

---

Summary of Model Fitting Results

```
      AIC       BIC    logLik
 29.88308  34.94972 -11.94154

Coefficients:
       Value   Std.Error
A 9.96431225 0.068802367
m 0.09800335 0.004590925

Correlation:
          A         m
A 1.0000000 0.5512196
m 0.5512196 1.0000000

Approximate 95% confidence intervals

 Coefficients:
       lower       est.      upper
A 9.82599808 9.96431225 10.1045734
m 0.08913658 0.09800335  0.1077521

 Residual standard error:
    lower      est.     upper
0.3007063 0.3679508 0.4742069

Degrees of freedom: 40 total; 38 residual
```



Goodness of Fit

The chi-squared goodness-of-fit values should be taken as general indications of fit only. P-values are likely to be inaccurate to some degree

Pearson Chi-Square Statistic: 27.03 with 2 degrees of freedom. P = 1.35e-06

	dose	n	chei	Expected	sd	Exp.SD	X2 Resid.
1	0.00	10	9.5	9.964312	0.3	0.3627374	-4.0477888
2	0.03	10	10.1	9.935059	0.1	0.3616843	1.4421101
3	0.30	10	10.0	9.675616	0.2	0.3523434	2.9113406
4	3.00	10	7.4	7.426093	0.1	0.2712255	-0.3042235

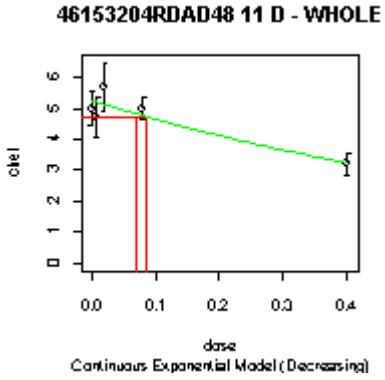
WARNING: Predicted Standard Deviations deviate substantially from the observed ones!

```
------------------------------------------------------------------
                        BMD Computation

                  BMD = 1.075:  BMDL = 0.9982

------------------------------------------------------------------
                        Potency Measures

A unit dose (1 mg/kg) would result in 100*exp(-Potency)% of background
activity

Potency: 0.098
se: 0.004591
var=se^2: 2.108e-05
Per cent. of background at unit dose: 91
Per cent. of background at the highest dose: 75
ED50 (95% CI): 7.073 ( 6.452 , 7.753 )

ln(Potency) -2.323
se[log(Potency)]: 0.04684
```
se[log(Potency)]^2: 0.002194

4. Dicrotophos

a. Adult, Repeated

```
                DICROTOPHOS:11-D:BRAIN:F:WHOLE
                    Fri Jan 04 12:53:17 1980
          MRID: 46153204RDAD48   Guideline: NONGUIDELINE
            Continuous Exponential Model (Decreasing)
            Formula: chei = B + (A-B)*exp(-(m*dose)^g)

Variance Function: power


   The BMD corresponds to a dose that results in a 10% reduction in the
                    response relative to the control
    ------------------------------------------------------------------
                    Summary of Model Fitting Results

      AIC       BIC    logLik
 44.28351  47.94014 -19.14176

Coefficients:
     Value Std.Error
A 5.261217 0.1471595
m 1.215822 0.1553200

Correlation:
          A         m
A 1.0000000 0.5514934
m 0.5514934 1.0000000

Approximate 95% confidence intervals

 Coefficients:
      lower     est.    upper
A 4.9654339 5.261217 5.574619
m 0.9334681 1.215822 1.583582

 Residual standard error:
    lower      est.     upper
0.5161955 0.6641617 0.9316598

Degrees of freedom: 25 total; 23 residual
    ------------------------------------------------------------------
                            Goodness of Fit
 The chi-squared goodness-of-fit values should be taken as general
indications of fit only.  P-values are likely to be inaccurate to some
degree

Pearson Chi-Square Statistic: 9.861 with 3 degrees of freedom.  P =
0.0198
```



```
   dose n chei Expected   sd    Exp.SD  X2 Resid.
1 0.000 5 5.01 5.261217 0.45 0.6107063 -0.9198163
2 0.008 5 4.70 5.210291 0.53 0.6050374 -1.8859093
3 0.020 5 5.70 5.134826 0.65 0.5966326  2.1181686
4 0.080 5 5.01 4.773580 0.30 0.5563278  0.9502513
5 0.400 5 3.19 3.235015 0.27 0.3831105 -0.2627336

    ------------------------------------------------------------------
                            BMD Computation

                    BMD = 0.08666:  BMDL = 0.07161

    ------------------------------------------------------------------
                            Potency Measures

A unit dose (1 mg/kg) would result in 100*exp(-Potency)% of background
activity

Potency: 1.216
se: 0.1553
var=se^2: 0.02412
Per cent. of background at unit dose: 30
Per cent. of background at the highest dose: 61
ED50 (95% CI): 0.5701 ( 0.4438 , 0.7323 )

ln(Potency) 0.1954
se[log(Potency)]: 0.1277
se[log(Potency)]^2: 0.01632
```

DICROTOPHOS:11-D:BRAIN:M:WHOLE
Fri Jan 04 12:53:27 1980
MRID: 46153204RDAD48 Guideline: NONGUIDELINE
Continuous Exponential Model (Decreasing)
Formula: chei = B + (A-B)*exp(-(m*dose)^g)

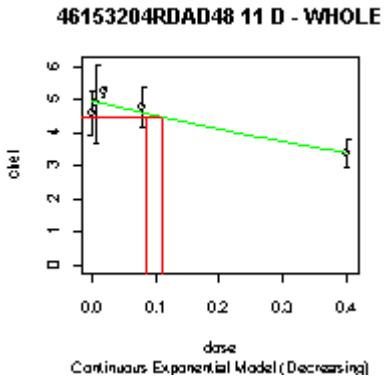
Variance Function: power

The BMD corresponds to a dose that results in a 10% reduction in the response relative to the control

---

Summary of Model Fitting Results

```
      AIC       BIC    logLik
 45.95487  49.61150 -19.97744

Coefficients:
      Value Std.Error
A 4.9754007 0.1485699
m 0.9641208 0.1647604

Correlation:
          A         m
A 1.0000000 0.5535611
m 0.5535611 1.0000000

Approximate 95% confidence intervals

 Coefficients:
      lower      est.    upper
A 4.6773605 4.9754007 5.292432
m 0.6770194 0.9641208 1.372972

 Residual standard error:
    lower      est.     upper
0.5061113 0.6511868 0.9134593

Degrees of freedom: 25 total; 23 residual
```



Goodness of Fit

The chi-squared goodness-of-fit values should be taken as general indications of fit only. P-values are likely to be inaccurate to some degree

Pearson Chi-Square Statistic: 4.33 with 3 degrees of freedom. P = 0.228

	dose	n	chei	Expected	sd	Exp.SD	X2 Resid.
1	0.000	5	4.57	4.975401	0.54	0.6169182	-1.4694063
2	0.008	5	4.87	4.937173	0.97	0.6123144	-0.2453052
3	0.020	5	5.24	4.880382	0.13	0.6054729	1.3281027
4	0.080	5	4.75	4.606076	0.48	0.5723953	0.5622415
5	0.400	5	3.35	3.383320	0.34	0.4241992	-0.1756407

BMD Computation

BMD = 0.1093: BMDL = 0.0853

Potency Measures

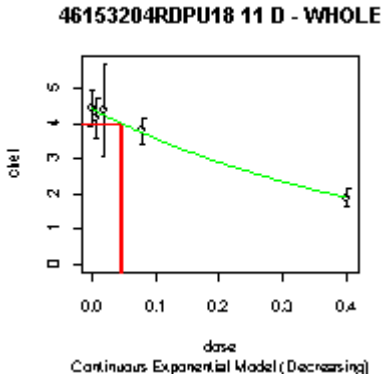
A unit dose (1 mg/kg) would result in 100*exp(-Potency)% of background activity

Potency: 0.9641
se: 0.1648
var=se^2: 0.02715
Per cent. of background at unit dose: 38
Per cent. of background at the highest dose: 68
ED50 (95% CI): 0.7189 (0.5143 , 1.005)

ln(Potency) -0.03654
se[log(Potency)]: 0.1709
se[log(Potency)]^2: 0.0292

b. Pup, Repeated

```
                    DICROTOPHOS:11-D:BRAIN:F:WHOLE
                        Fri Jan 04 12:53:36 1980
                MRID: 46153204RDPU18   Guideline: NONGUIDELINE
                  Continuous Exponential Model (Decreasing)
                  Formula: chei = B + (A-B)*exp(-(m*dose)^g)

Variance Function: power


   The BMD corresponds to a dose that results in a 10% reduction in the
                    response relative to the control
    ------------------------------------------------------------------
                    Summary of Model Fitting Results

      AIC       BIC    logLik
 38.62325  42.27987 -16.31162

Coefficients:
     Value Std.Error
A 4.437535 0.1443560
m 2.125542 0.1795871

Correlation:
          A         m
A 1.0000000 0.5533875
m 0.5533875 1.0000000

Approximate 95% confidence intervals

 Coefficients:
     lower     est.    upper
A 4.148739 4.437535 4.746436
m 1.784692 2.125542 2.531489

 Residual standard error:
    lower      est.     upper
0.4690526 0.6035055 0.8465737

Degrees of freedom: 25 total; 23 residual
    ------------------------------------------------------------------
                              Goodness of Fit
 The chi-squared goodness-of-fit values should be taken as general
indications of fit only.  P-values are likely to be inaccurate to some
degree

Pearson Chi-Square Statistic: 1.139 with 3 degrees of freedom.  P =
0.768
```



	dose	n	chei	Expected	sd	Exp.SD	X2 Resid.
1	0.000	5	4.46	4.437535	0.41	0.5993913	0.08380527
2	0.008	5	4.14	4.362716	0.46	0.5894251	-0.84490522
3	0.020	5	4.41	4.252846	1.07	0.5747855	0.61137221
4	0.080	5	3.79	3.743630	0.29	0.5068645	0.20456332
5	0.400	5	1.89	1.896258	0.20	0.2591895	-0.05398726

BMD Computation

BMD = 0.04957: BMDL = 0.04352

Potency Measures

A unit dose (1 mg/kg) would result in 100*exp(-Potency)% of background activity

Potency: 2.126
se: 0.1796
var=se^2: 0.03225
Per cent. of background at unit dose: 12
Per cent. of background at the highest dose: 43
ED50 (95% CI): 0.3261 (0.2763 , 0.3848)

ln(Potency) 0.754
se[log(Potency)]: 0.08449
se[log(Potency)]^2: 0.007139

DICROTOPHOS:11-D:BRAIN:M:WHOLE
Fri Jan 04 12:53:44 1980
MRID: 46153204RDPU18 Guideline: NONGUIDELINE
Continuous Exponential Model (Decreasing)
Formula: chei = B + (A-B)*exp(-(m*dose)^g)

Variance Function: power

The BMD corresponds to a dose that results in a 10% reduction in the response relative to the control

---

Summary of Model Fitting Results

AIC	BIC	logLik
63.67557	67.33220	-28.83779

Coefficients:

	Value	Std.Error
A	4.655131	0.2271053
m	1.641164	0.2680060

Correlation:

	A	m
A	1.000000	0.554989
m	0.554989	1.000000

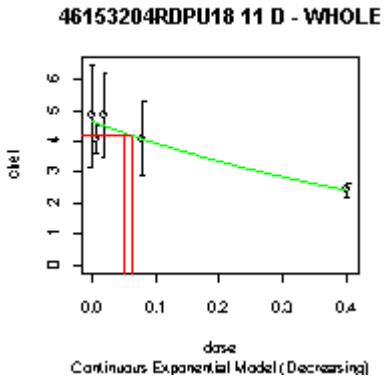
Approximate 95% confidence intervals

Coefficients:

	lower	est.	upper
A	4.208257	4.655131	5.149459
m	1.170685	1.641164	2.300721

Residual standard error:

lower	est.	upper
0.7645667	0.9837279	1.3799348



Degrees of freedom: 25 total; 23 residual

Goodness of Fit

The chi-squared goodness-of-fit values should be taken as general indications of fit only. P-values are likely to be inaccurate to some degree

Pearson Chi-Square Statistic: 2.554 with 3 degrees of freedom. P = 0.466

	dose	n	chei	Expected	sd	Exp.SD	X2 Resid.
1	0.000	5	4.84	4.655131	1.34	0.9434034	0.43817865
2	0.008	5	4.06	4.594412	0.38	0.9311911	-1.28328282
3	0.020	5	4.85	4.504815	1.11	0.9131683	0.84525197
4	0.080	5	4.09	4.082367	0.95	0.8281537	0.02060974
5	0.400	5	2.41	2.414529	0.18	0.4917732	-0.02059499

BMD Computation

BMD = 0.0642: BMDL = 0.05061

Potency Measures

A unit dose (1 mg/kg) would result in 100*exp(-Potency)% of background activity

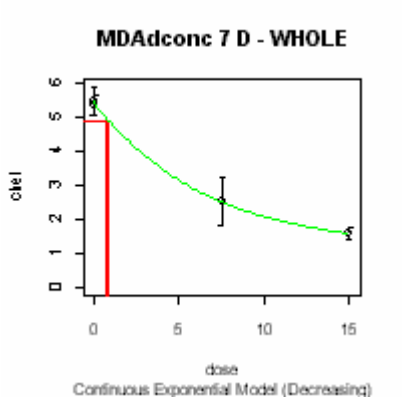
Potency: 1.641
se: 0.268
var=se^2: 0.07183
Per cent. of background at unit dose: 19
Per cent. of background at the highest dose: 52
ED50 (95% CI): 0.4224 (0.3067 , 0.5817)

ln(Potency) 0.4954
se[log(Potency)]: 0.1633
se[log(Potency)]^2: 0.02667

5. DDVP

a. Adult, Repeated, Concurrent

```
                    DDVP:7-D:BRAIN:F:WHOLE
                   Mon Apr 24 21:43:34 2006
          MRID: MDAdconc   Guideline: NONGUIDELINE
        Continuous Exponential Model (Decreasing)
        Formula: chei = B + (A-B)*exp(-(m*dose)^g)

Variance Function: power


   The BMD corresponds to a dose that results in a 10% reduction in the
                    response relative to the control
    ------------------------------------------------------------------
                    Summary of Model Fitting Results

     AIC      BIC   logLik
25.51746 29.50039 -8.75873

Coefficients:
      Value  Std.Error
A 5.4680592 0.21623032
B 1.1331342 0.27076016
m 0.1529701 0.03053395

Correlation:
          A         B         m
A 1.0000000 0.1901865 0.3377826
B 0.1901865 1.0000000 0.9369459
m 0.3377826 0.9369459 1.0000000

Approximate 95% confidence intervals

 Coefficients:
      lower      est.     upper
A 5.0303656 5.4680592 5.9438367
B 0.6844438 1.1331342 1.8759659
m 0.1003945 0.1529701 0.2330789

 Residual standard error:
    lower      est.     upper
0.5119114 0.6821960 1.0227101

Degrees of freedom: 20 total; 17 residual
    ------------------------------------------------------------------
                              Goodness of Fit
 The chi-squared goodness-of-fit values should be taken as general
indications of fit only.  P-values are likely to be inaccurate to some
degree
```



Pearson Chi-Square Statistic: 0.03915 with 1 degrees of freedom. P = 0.843

	dose	n	chei	Expected	sd	Exp.SD	X2 Resid.
1	0.0	5	5.51	5.468059	0.34	0.6770768	0.138510867
2	0.1	5	5.36	5.402252	0.25	0.6689085	-0.141243990
3	7.5	5	2.51	2.509476	0.56	0.3104510	0.003776490
4	15.0	5	1.57	1.570124	0.15	0.1945313	-0.001419862

BMD Computation

BMD = 0.8814: BMDL = 0.713

Potency Measures

A unit dose (1 mg/kg) would result in 100*exp(-Potency)% of background activity

Potency: 0.153
se: 0.03053
var=se^2: 0.0009323
Per cent. of background at unit dose: 86
Per cent. of background at the highest dose: 10
ED50 (95% CI): 4.531 (3.064 , 6.701)

ln(Potency) -1.878
se[log(Potency)]: 0.1996
se[log(Potency)]^2: 0.03984

DDVP:7-D:BRAIN:M:WHOLE
Mon Apr 24 21:43:40 2006
MRID: MDAdconc Guideline: NONGUIDELINE
Continuous Exponential Model (Decreasing)
Formula: chei = B + (A-B)*exp(-(m*dose)^g)

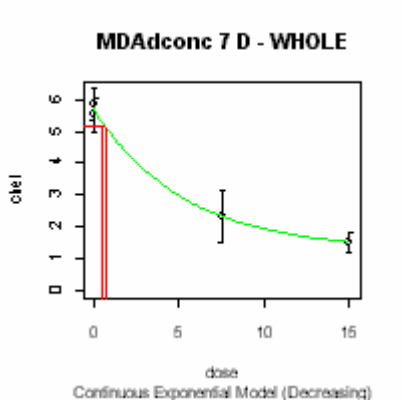
Variance Function: power

The BMD corresponds to a dose that results in a 10% reduction in the response relative to the control

---

Summary of Model Fitting Results

```
      AIC       BIC    logLik
 38.65735  42.64027 -15.32867

Coefficients:
      Value  Std.Error
A 5.7226764 0.31678214
B 1.2589525 0.25158074
m 0.1917306 0.04343782

Correlation:
          A         B         m
A 1.0000000 0.1403111 0.3067966
B 0.1403111 1.0000000 0.8887349
m 0.3067966 0.8887349 1.0000000
```




```
Approximate 95% confidence intervals

 Coefficients:
      lower      est.     upper
A 5.0918770 5.7226764 6.4316216
B 0.8258587 1.2589525 1.9191677
m 0.1188781 0.1917306 0.3092295

 Residual standard error:
    lower      est.     upper
0.7591362 1.0116588 1.5166222

Degrees of freedom: 20 total; 17 residual
```

Goodness of Fit

```
 The chi-squared goodness-of-fit values should be taken as general
indications of fit only.  P-values are likely to be inaccurate to some
degree

Pearson Chi-Square Statistic: 0.1429 with 1 degrees of freedom.  P =
0.705

  dose n chei Expected   sd    Exp.SD    X2 Resid.
1  0.0 5 5.84 5.722676 0.40 0.9917110  0.264536182
2  0.1 5 5.52 5.637908 0.42 0.9768860 -0.269889484
3  7.5 5 2.32 2.318672 0.68 0.4003437  0.007418733
4 15.0 5 1.51 1.510537 0.26 0.2624115 -0.004578106
```

BMD Computation

BMD = 0.7156: BMDL = 0.551

Potency Measures

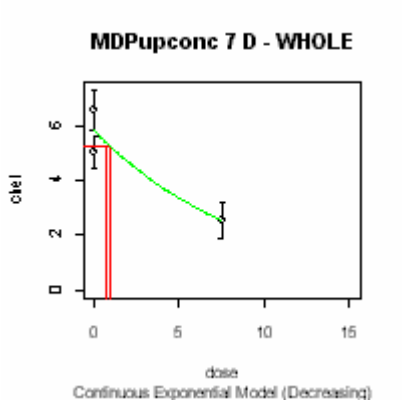
A unit dose (1 mg/kg) would result in 100*exp(-Potency)% of background activity

Potency: 0.1917
se: 0.04344
var=se^2: 0.001887
Per cent. of background at unit dose: 83
Per cent. of background at the highest dose: 5.6
ED50 (95% CI): 3.615 (2.319 , 5.636)

ln(Potency) -1.652
se[log(Potency)]: 0.2266
se[log(Potency)]^2: 0.0513

b. Pup, Repeated, Concurrent

```
                    DDVP:7-D:BRAIN:F:WHOLE
                    Mon Apr 24 21:43:59 2006
          MRID: MDPupconc   Guideline: NONGUIDELINE
          Continuous Exponential Model (Decreasing)
          Formula: chei = B + (A-B)*exp(-(m*dose)^g)

Variance Function: power

Highest 1 doses dropped from data set.


   The BMD corresponds to a dose that results in a 10% reduction in the
                    response relative to the control
    ------------------------------------------------------------------
                    Summary of Model Fitting Results

      AIC       BIC    logLik
 39.29316  41.41732 -16.64658

Coefficients:
      Value  Std.Error
A 5.8381055 0.33369886
m 0.1111981 0.01312090

Correlation:
          A         m
A 1.0000000 0.5883474
m 0.5883474 1.0000000

Approximate 95% confidence intervals

 Coefficients:
       lower      est.     upper
A 5.15992657 5.8381055 6.6054187
m 0.08617663 0.1111981 0.1434846

 Residual standard error:
    lower      est.     upper
0.8565106 1.1814689 1.9033966

Degrees of freedom: 15 total; 13 residual
    ------------------------------------------------------------------
                              Goodness of Fit
 The chi-squared goodness-of-fit values should be taken as general
indications of fit only.  P-values are likely to be inaccurate to some
degree

Pearson Chi-Square Statistic: 5.215 with 1 degrees of freedom.  P =
0.0224
```



	dose	n	chei	Expected	sd	Exp.SD	X2 Resid.
1	0.0	5	6.59	5.838105	0.59	1.0482540	1.60389304
2	0.1	5	5.02	5.773546	0.46	1.0365378	-1.62558583
3	7.5	5	2.54	2.535575	0.54	0.4511931	0.02192763

BMD Computation

BMD = 0.9475: BMDL = 0.7935

Potency Measures

A unit dose (1 mg/kg) would result in 100*exp(-Potency)% of background activity

Potency: 0.1112
se: 0.01312
var=se^2: 0.0001722
Per cent. of background at unit dose: 89
Per cent. of background at the highest dose: 43
ED50 (95% CI): 6.233 (4.946 , 7.855)

ln(Potency) -2.196
se[log(Potency)]: 0.118
se[log(Potency)]^2: 0.01392

DDVP:7-D:BRAIN:M:WHOLE
Mon Apr 24 21:44:06 2006
MRID: MDPupconc Guideline: NONGUIDELINE
Continuous Exponential Model (Decreasing)
Formula: chei = B + (A-B)*exp(-(m*dose)^g)

Variance Function: power

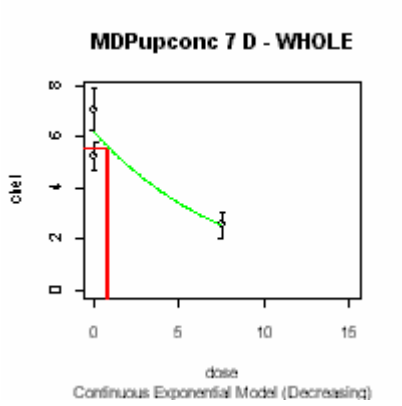
Highest 1 doses dropped from data set.

The BMD corresponds to a dose that results in a 10% reduction in the response relative to the control

---

Summary of Model Fitting Results

```
      AIC       BIC    logLik
 38.62180  40.74595 -16.31090

Coefficients:
      Value  Std.Error
A 6.2176817 0.33406064
m 0.1201434 0.01231365

Correlation:
         A        m
A 1.000000 0.589248
m 0.589248 1.000000

Approximate 95% confidence intervals

 Coefficients:
       lower      est.     upper
A 5.53629700 6.2176817 6.9829285
m 0.09628064 0.1201434 0.1499205

 Residual standard error:
    lower      est.     upper
0.8659536 1.1944947 1.9243816

Degrees of freedom: 15 total; 13 residual
```



Goodness of Fit

The chi-squared goodness-of-fit values should be taken as general indications of fit only. P-values are likely to be inaccurate to some degree

Pearson Chi-Square Statistic: 7.004 with 1 degrees of freedom. P = 0.00813

	dose	n	chei	Expected	sd	Exp.SD	X2 Resid.
1	0.0	5	7.09	6.217682	0.64	1.0494073	1.85872816
2	0.1	5	5.27	6.143427	0.44	1.0367170	-1.88387271
3	7.5	5	2.53	2.525203	0.41	0.4213597	0.02545729

BMD Computation

BMD = 0.877: BMDL = 0.7504

Potency Measures

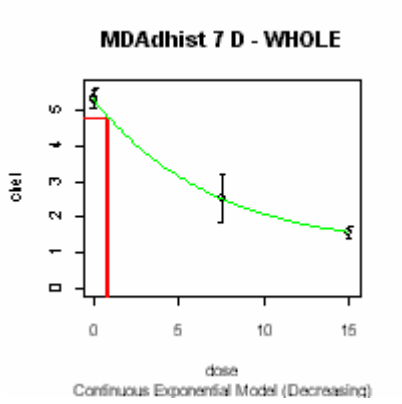
A unit dose (1 mg/kg) would result in 100*exp(-Potency)% of background activity

Potency: 0.1201
se: 0.01231
var=se^2: 0.0001516
Per cent. of background at unit dose: 89
Per cent. of background at the highest dose: 41
ED50 (95% CI): 5.769 (4.719 , 7.053)

ln(Potency) -2.119
se[log(Potency)]: 0.1025
se[log(Potency)]^2: 0.0105

c. Adult, Repeated, Historical

```
                    DDVP:7-D:BRAIN:F:WHOLE
                    Mon Apr 24 21:43:45 2006
          MRID: MDAdhist   Guideline: NONGUIDELINE
        Continuous Exponential Model (Decreasing)
        Formula: chei = B + (A-B)*exp(-(m*dose)^g)

Variance Function: power


   The BMD corresponds to a dose that results in a 10% reduction in the
                    response relative to the control
    ------------------------------------------------------------------
                    Summary of Model Fitting Results

      AIC       BIC    logLik
 64.04178  70.79730 -28.02089

Coefficients:
      Value  Std.Error
A 5.3368308 0.11905590
B 1.0997356 0.28281397
m 0.1465709 0.02915622

Correlation:
          A         B         m
A 1.0000000 0.1150917 0.2036726
B 0.1150917 1.0000000 0.9481542
m 0.2036726 0.9481542 1.0000000

Approximate 95% confidence intervals

 Coefficients:
       lower      est.     upper
A 5.10097136 5.3368308 5.5835960
B 0.65311837 1.0997356 1.8517598
m 0.09794975 0.1465709 0.2193271

 Residual standard error:
    lower      est.     upper
0.5322331 0.6528354 0.8446040

Degrees of freedom: 40 total; 37 residual
    ------------------------------------------------------------------
                              Goodness of Fit
 The chi-squared goodness-of-fit values should be taken as general
indications of fit only.  P-values are likely to be inaccurate to some
degree

Pearson Chi-Square Statistic: 0.104 with 1 degrees of freedom.  P =
0.747
```



	dose	n	chei	Expected	sd	Exp.SD	X2 Resid.
1	0.0	25	5.32	5.336831	0.60	0.6499687	-0.129474129
2	0.1	5	5.36	5.275180	0.25	0.6424933	0.295197982
3	7.5	5	2.51	2.511155	0.56	0.3062988	-0.008433535
4	15.0	5	1.57	1.569894	0.15	0.1909515	0.001242926

BMD Computation

BMD = 0.9185: BMDL = 0.7518

Potency Measures

A unit dose (1 mg/kg) would result in 100*exp(-Potency)% of background activity

Potency: 0.1466
se: 0.02916
var=se^2: 0.0008501
Per cent. of background at unit dose: 86
Per cent. of background at the highest dose: 11
ED50 (95% CI): 4.729 (3.202 , 6.984)

ln(Potency) -1.92
se[log(Potency)]: 0.1989
se[log(Potency)]^2: 0.03957

DDVP:7-D:BRAIN:M:WHOLE
Mon Apr 24 21:43:52 2006
MRID: MDAdhist Guideline: NONGUIDELINE
Continuous Exponential Model (Decreasing)
Formula: chei = B + (A-B)*exp(-(m*dose)^g)

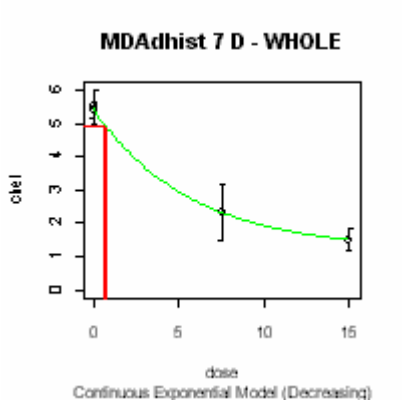
Variance Function: power

The BMD corresponds to a dose that results in a 10% reduction in the response relative to the control

---

Summary of Model Fitting Results

```
      AIC       BIC    logLik
 78.62698  85.38250 -35.31349

Coefficients:
      Value  Std.Error
A 5.4406635 0.14572755
B 1.2233684 0.23205212
m 0.1793503 0.03602974

Correlation:
           A          B         m
A 1.00000000 0.08852252 0.1851917
B 0.08852252 1.00000000 0.9107214
m 0.18519170 0.91072141 1.0000000

Approximate 95% confidence intervals

 Coefficients:
      lower      est.     upper
A 5.1532609 5.4406635 5.7440950
B 0.8329963 1.2233684 1.7966830
m 0.1193784 0.1793503 0.2694501

 Residual standard error:
    lower      est.     upper
0.6580918 0.8072133 1.0443300

Degrees of freedom: 40 total; 37 residual
```



Goodness of Fit

The chi-squared goodness-of-fit values should be taken as general indications of fit only. P-values are likely to be inaccurate to some degree

Pearson Chi-Square Statistic: 0.2307 with 1 degrees of freedom. P = 0.631

	dose	n	chei	Expected	sd	Exp.SD	X2 Resid.
1	0.0	25	5.41	5.440664	0.61	0.7954922	-0.192733152
2	0.1	5	5.52	5.365700	0.42	0.7846436	0.439720961
3	7.5	5	2.32	2.322001	0.68	0.3407920	-0.013132451
4	15.0	5	1.51	1.509570	0.26	0.2200316	0.004374445

BMD Computation

BMD = 0.7701: BMDL = 0.6168

Potency Measures

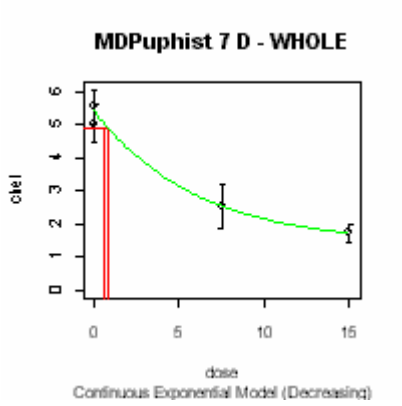
A unit dose (1 mg/kg) would result in 100*exp(-Potency)% of background activity

Potency: 0.1794
se: 0.03603
var=se^2: 0.001298
Per cent. of background at unit dose: 84
Per cent. of background at the highest dose: 6.8
ED50 (95% CI): 3.865 (2.607 , 5.73)

ln(Potency) -1.718
se[log(Potency)]: 0.2009
se[log(Potency)]^2: 0.040

d. Pup, Repeated, Historical

```
                    DDVP:7-D:BRAIN:F:WHOLE
                    Mon Apr 24 21:44:12 2006
          MRID: MDPuphist   Guideline: NONGUIDELINE
          Continuous Exponential Model (Decreasing)
          Formula: chei = B + (A-B)*exp(-(m*dose)^g)

Variance Function: power


   The BMD corresponds to a dose that results in a 10% reduction in the
                    response relative to the control
    ------------------------------------------------------------------
                    Summary of Model Fitting Results

      AIC       BIC    logLik
 91.73904  98.07312 -41.86952

Coefficients:
      Value  Std.Error
A 5.4535860 0.20843990
B 1.3874190 0.37759636
m 0.1686908 0.05235096

Correlation:
          A         B         m
A 1.0000000 0.0969725 0.1952096
B 0.0969725 1.0000000 0.9213612
m 0.1952096 0.9213612 1.0000000

Approximate 95% confidence intervals

 Coefficients:
       lower      est.     upper
A 5.04558081 5.4535860 5.8945841
B 0.79750815 1.3874190 2.4136825
m 0.08971903 0.1686908 0.3171746

 Residual standard error:
   lower     est.    upper
0.867120 1.075062 1.415080

Degrees of freedom: 36 total; 33 residual
    ------------------------------------------------------------------
                             Goodness of Fit
 The chi-squared goodness-of-fit values should be taken as general
indications of fit only.  P-values are likely to be inaccurate to some
degree

Pearson Chi-Square Statistic: 0.7522 with 1 degrees of freedom.  P =
0.386
```



	dose	n	chei	Expected	sd	Exp.SD	X2 Resid.
1	0.0	21	5.54	5.453586	1.18	1.0587084	0.374039299
2	0.1	5	5.02	5.385569	0.46	1.0451764	-0.782104088
3	7.5	5	2.54	2.534843	0.54	0.4881430	0.023622823
4	15.0	5	1.71	1.711208	0.22	0.3342521	-0.008084159

BMD Computation

BMD = 0.8537: BMDL = 0.6228

Potency Measures

A unit dose (1 mg/kg) would result in 100*exp(-Potency)% of background activity

Potency: 0.1687
se: 0.05235
var=se^2: 0.002741
Per cent. of background at unit dose: 84
Per cent. of background at the highest dose: 8
ED50 (95% CI): 4.109 (2.237 , 7.549)

ln(Potency) -1.78
se[log(Potency)]: 0.3103
se[log(Potency)]^2: 0.09631

DDVP:7-D:BRAIN:M:WHOLE
Mon Apr 24 21:44:18 2006
MRID: MDPuphist Guideline: NONGUIDELINE
Continuous Exponential Model (Decreasing)
Formula: chei = B + (A-B)*exp(-(m*dose)^g)

Variance Function: power

The BMD corresponds to a dose that results in a 10% reduction in the response relative to the control

---

Summary of Model Fitting Results

AIC	BIC	logLik
90.63050	97.28474	-41.31525

Coefficients:

	Value	Std.Error
A	5.6883165	0.17732604
B	1.1782553	0.33427136
m	0.1610776	0.03905932

Correlation:

	A	B	m
A	1.0000000	0.1065217	0.2028358
B	0.1065217	1.0000000	0.9324765
m	0.2028358	0.9324765	1.0000000

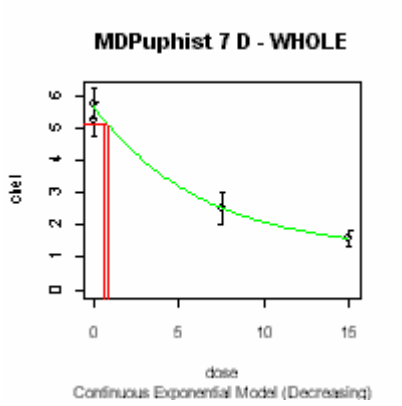
Approximate 95% confidence intervals

Coefficients:

	lower	est.	upper
A	5.33981535	5.6883165	6.059562
B	0.66276419	1.1782553	2.094690
m	0.09850411	0.1610776	0.263400

Residual standard error:

lower	est.	upper
0.7834716	0.9634302	1.2514578



Degrees of freedom: 39 total; 36 residual

Goodness of Fit

The chi-squared goodness-of-fit values should be taken as general indications of fit only. P-values are likely to be inaccurate to some degree

Pearson Chi-Square Statistic: 0.8159 with 1 degrees of freedom. P = 0.366

	dose	n	chei	Expected	sd	Exp.SD	X2 Resid.
1	0.0	24	5.76	5.688316	1.05	0.9517421	0.36898250
2	0.1	5	5.27	5.616251	0.44	0.9394402	-0.82415231
3	7.5	5	2.53	2.525726	0.41	0.4194838	0.02278489
4	15.0	5	1.58	1.580839	0.21	0.2660983	-0.00704853

BMD Computation

BMD = 0.837: BMDL = 0.6514

Potency Measures

A unit dose (1 mg/kg) would result in 100*exp(-Potency)% of background activity

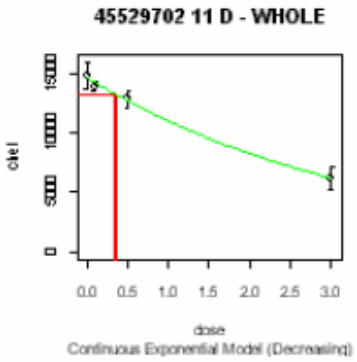
Potency: 0.1611
se: 0.03906
var=se^2: 0.001526
Per cent. of background at unit dose: 85
Per cent. of background at the highest dose: 8.9
ED50 (95% CI): 4.303 (2.675 , 6.921)

ln(Potency) -1.826
se[log(Potency)]: 0.2425
se[log(Potency)]^2: 0.0588

6. Dimethoate

a. Adult, Repeated

```
                    DIMETHOATE:11-D:BRAIN:F:WHOLE
                     Wed Aug 18 18:39:56 2004
                MRID: 45529702   Guideline: NONGUIDELINE
               Continuous Exponential Model (Decreasing)
               Formula: chei = B + (A-B)*exp(-(m*dose)^g)

Variance Function: power


   The BMD corresponds to a dose that results in a 10% reduction in the
                       response relative to the control
    ------------------------------------------------------------------
                       Summary of Model Fitting Results

      AIC       BIC    logLik
 546.8830  551.2802 -270.4415

Coefficients:
         Value     Std.Error
A 1.467991e+04 331.88894597
m 2.875262e-01   0.01490362

Correlation:
          A         m
A 1.0000000 0.5903737
m 0.5903737 1.0000000

Approximate 95% confidence intervals

 Coefficients:
         lower          est.         upper
A 1.401751e+04 1.467991e+04 1.537360e+04
m 2.586446e-01 2.875262e-01 3.196329e-01

 Residual standard error:
   lower     est.    upper
1225.850 1534.016 2050.478

Degrees of freedom: 32 total; 30 residual
    ------------------------------------------------------------------
                              Goodness of Fit
 The chi-squared goodness-of-fit values should be taken as general
indications of fit only.  P-values are likely to be inaccurate to some
degree

Pearson Chi-Square Statistic: 0.7123 with 2 degrees of freedom.  P =
0.7

  dose n      chei  Expected        sd    Exp.SD   X2 Resid.
1  0.0 8 14868.75 14679.905 1399.7289 1513.3442  0.35294916
2  0.1 8 13912.50 14263.830  446.2142 1470.6675 -0.67568682
3  0.5 8 12881.25 12714.161  845.1278 1311.6610  0.36030474
4  3.0 8  6187.50  6195.981 1077.6131  641.5657 -0.03738933
```



BMD Computation

BMD = 0.3664: BMDL = 0.3377

Potency Measures

A unit dose (1 mg/kg) would result in 100*exp(-Potency)% of background activity

Potency: 0.2875
se: 0.0149
var=se^2: 0.0002221
Per cent. of background at unit dose: 75
Per cent. of background at the highest dose: 42
ED50 (95% CI): 2.411 (2.178 , 2.669)

ln(Potency) -1.246
se[log(Potency)]: 0.05183
se[log(Potency)]^2: 0.002687

DIMETHOATE:11-D:BRAIN:M:WHOLE
Wed Aug 18 18:40:01 2004
MRID: 45529702 Guideline: NONGUIDELINE
Continuous Exponential Model (Decreasing)
Formula: chei = B + (A-B)*exp(-(m*dose)^g)

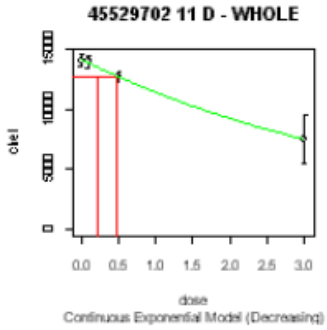
Variance Function: power

The BMD corresponds to a dose that results in a 10% reduction in the response relative to the control

---

Summary of Model Fitting Results

```
      AIC       BIC    logLik
 580.8117  586.6747 -286.4059

Coefficients:
         Value     Std.Error
A 1.418582e+04 6.693422e+02
B 6.934757e+02 2.463564e+04
m 2.295838e-01 6.112029e-01

Correlation:
          A         B         m
A 1.0000000 0.6252848 0.6441556
B 0.6252848 1.0000000 0.9990744
m 0.6441556 0.9990744 1.0000000

Approximate 95% confidence intervals

 Coefficients:
         lower          est.         upper
A 1.288084e+04 1.418582e+04 1.562301e+04
B 1.935073e-29 6.934757e+02 2.485221e+34
m 9.914506e-04 2.295838e-01 5.316323e+01

 Residual standard error:
   lower     est.    upper
1881.485 2362.467 3175.900

Degrees of freedom: 32 total; 29 residual
```



Goodness of Fit

The chi-squared goodness-of-fit values should be taken as general indications of fit only. P-values are likely to be inaccurate to some degree

Pearson Chi-Square Statistic: 0.02856 with 1 degrees of freedom. P = 0.866

	dose	n	chei	Expected	sd	Exp.SD	X2 Resid.
1	0.0	8	14100.00	14185.82	529.1503	2376.373	-0.102149399
2	0.1	8	13987.50	13879.59	661.5728	2325.356	0.131255835
3	0.5	8	12700.00	12722.60	547.7226	2132.402	-0.029977672
4	3.0	8	7468.75	7469.37	2484.3708	1251.247	-0.001401282

BMD Computation

BMD = 0.4839: BMDL = 0.2183

Potency Measures

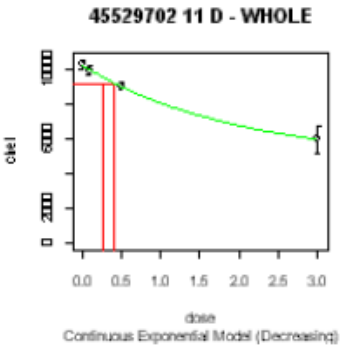
A unit dose (1 mg/kg) would result in 100*exp(-Potency)% of background activity

Potency: 0.2296
se: 0.6112
var=se^2: 0.3736
Per cent. of background at unit dose: 79
Per cent. of background at the highest dose: 50
ED50 (95% CI): 3.019 (0.01636 , 557.2)

ln(Potency) -1.471
se[log(Potency)]: 2.662
se[log(Potency)]^2: 7.087

b. Pup, Repeated

```
                    DIMETHOATE:11-D:BRAIN:F:WHOLE
                       Wed Aug 18 20:12:24 2004
                 MRID: 45529702   Guideline: NONGUIDELINE
               Continuous Exponential Model (Decreasing)
               Formula: chei = B + (A-B)*exp(-(m*dose)^g)

Variance Function: power


   The BMD corresponds to a dose that results in a 10% reduction in the
                       response relative to the control
    ------------------------------------------------------------------
                       Summary of Model Fitting Results

     AIC      BIC    logLik
 517.114  522.977 -254.557

Coefficients:
         Value     Std.Error
A 1.023172e+04   244.4269786
B 4.761725e+03  1434.4099641
m 5.070756e-01     0.3102889

Correlation:
          A         B         m
A 1.0000000 0.5727942 0.6245823
B 0.5727942 1.0000000 0.9863055
m 0.6245823 0.9863055 1.0000000

Approximate 95% confidence intervals

 Coefficients:
         lower          est.         upper
A 9743.8245469 1.023172e+04 10744.040990
B 2571.5535403 4.761725e+03  8817.247872
m    0.1450599 5.070756e-01     1.772549

 Residual standard error:
    lower      est.     upper
 689.2430  865.4407 1163.4250

Degrees of freedom: 32 total; 29 residual
    ------------------------------------------------------------------
                                Goodness of Fit
 The chi-squared goodness-of-fit values should be taken as general
indications of fit only.  P-values are likely to be inaccurate to some
degree

Pearson Chi-Square Statistic: 0.05658 with 1 degrees of freedom.  P =
0.812

  dose n     chei  Expected       sd   Exp.SD    X2 Resid.
1  0.0 8 10275.00 10231.718 376.0699 861.9491  0.142027400
2  0.1 8  9906.25  9961.263 313.3204 839.0650 -0.185444384
3  0.5 8  9018.75  9006.715 247.7578 758.3745  0.044884938
4  3.0 8  5956.25  5956.611 964.8973 501.7452 -0.002033078
```



BMD Computation

BMD = 0.4084: BMDL = 0.2609

Potency Measures

A unit dose (1 mg/kg) would result in 100*exp(-Potency)% of background activity

Potency: 0.5071
se: 0.3103
var=se^2: 0.09628
Per cent. of background at unit dose: 60
Per cent. of background at the highest dose: 22
ED50 (95% CI): 1.367 (0.412 , 4.536)

ln(Potency) -0.6791
se[log(Potency)]: 0.6119
se[log(Potency)]^2: 0.3744

DIMETHOATE:11-D:BRAIN:M:WHOLE
Wed Aug 18 20:12:31 2004
MRID: 45529702 Guideline: NONGUIDELINE
Continuous Exponential Model (Decreasing)
Formula: chei = B + (A-B)*exp(-(m*dose)^g)

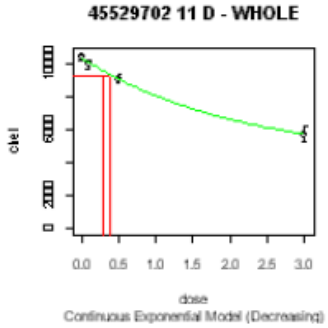
Variance Function: power

The BMD corresponds to a dose that results in a 10% reduction in the response relative to the control

---

Summary of Model Fitting Results

```
      AIC       BIC    logLik
 490.4541  496.3170 -241.2270
```



Coefficients:

```
         Value     Std.Error
A 1.030886e+04  163.3439882
B 4.209439e+03 1128.3793005
m 4.723459e-01    0.1929238
```

Correlation:

```
          A         B         m
A 1.0000000 0.5845660 0.6296056
B 0.5845660 1.0000000 0.9903008
m 0.6296056 0.9903008 1.0000000
```

Approximate 95% confidence intervals

Coefficients:

```
         lower          est.         upper
A 9980.1364087 1.030886e+04 10648.405296
B 2432.9062934 4.209439e+03  7283.213837
m    0.2048675 4.723459e-01     1.089049
```

Residual standard error:

```
   lower     est.    upper
462.2901 580.4697 780.3343
```

Degrees of freedom: 32 total; 29 residual

Goodness of Fit

The chi-squared goodness-of-fit values should be taken as general indications of fit only. P-values are likely to be inaccurate to some degree

Pearson Chi-Square Statistic: 0.2933 with 1 degrees of freedom. P = 0.588

```
  dose n      chei  Expected       sd   Exp.SD    X2 Resid.
1  0.0 8 10375.00 10308.857 207.0197 576.9300  0.324268111
2  0.1 8  9943.75 10027.452 331.0562 561.0777 -0.421947102
3  0.5 8  9043.75  9025.808 339.5769 504.7310  0.100541175
4  3.0 8  5687.50  5688.128 566.7892 318.2699 -0.005577083
```

BMD Computation

BMD = 0.392: BMDL = 0.2888

Potency Measures

A unit dose (1 mg/kg) would result in 100*exp(-Potency)% of background activity

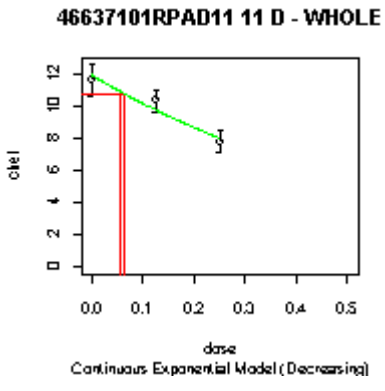
Potency: 0.4723
se: 0.1929
var=se^2: 0.03722
Per cent. of background at unit dose: 62
Per cent. of background at the highest dose: 24
ED50 (95% CI): 1.467 (0.659 , 3.268)

ln(Potency) -0.75
se[log(Potency)]: 0.4084
se[log(Potency)]^2: 0.1668

7. Disulfoton

a. Adult, Repeated

```
                    DISULFOTON:11-D:BRAIN:F:WHOLE
                        Fri Jan 04 19:39:29 1980
                MRID: 46637101RPAD11   Guideline: NONGUIDELINE
                  Continuous Exponential Model (Decreasing)
                  Formula: chei = B + (A-B)*exp(-(m*dose)^g)

Variance Function: power

Highest 1 doses dropped from data set.


   The BMD corresponds to a dose that results in a 10% reduction in the
                        response relative to the control
    ------------------------------------------------------------------
                        Summary of Model Fitting Results

      AIC       BIC    logLik
 48.50618  51.17729 -21.25309

Coefficients:
      Value Std.Error
A 11.915915 0.3775353
m  1.606323 0.1980217

Correlation:
          A         m
A 1.0000000 0.7701856
m 0.7701856 1.0000000

Approximate 95% confidence intervals

 Coefficients:
      lower      est.     upper
A 11.141862 11.915915 12.743744
m  1.236907  1.606323  2.086070

 Residual standard error:
    lower      est.     upper
0.7384417 0.9915032 1.5089975

Degrees of freedom: 18 total; 16 residual
    ------------------------------------------------------------------
                              Goodness of Fit
 The chi-squared goodness-of-fit values should be taken as general
indications of fit only.  P-values are likely to be inaccurate to some
degree

Pearson Chi-Square Statistic: 4.066 with 1 degrees of freedom.  P =
0.0438
```



	dose	n	chei	Expected	sd	Exp.SD	X2 Resid.
1	0.000	6	11.58	11.915915	0.912	1.0109023	-0.8139474
2	0.125	6	10.31	9.748218	0.650	0.8358384	1.6463453
3	0.250	6	7.74	7.974860	0.680	0.6910914	-0.8324332

BMD Computation

BMD = 0.06559: BMDL = 0.05453

Potency Measures

A unit dose (1 mg/kg) would result in 100*exp(-Potency)% of background activity

Potency: 1.606
se: 0.198
var=se^2: 0.03921
Per cent. of background at unit dose: 20
Per cent. of background at the highest dose: 67
ED50 (95% CI): 0.4315 (0.3389 , 0.5494)

ln(Potency) 0.4739
se[log(Potency)]: 0.1233
se[log(Potency)]^2: 0.0152

DISULFOTON:11-D:BRAIN:M:WHOLE
Fri Jan 04 19:39:39 1980
MRID: 46637101RPAD11 Guideline: NONGUIDELINE
Continuous Exponential Model (Decreasing)
Formula: chei = B + (A-B)*exp(-(m*dose)^g)

Variance Function: power

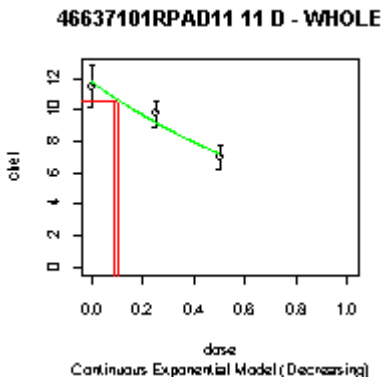
Highest 1 doses dropped from data set.

The BMD corresponds to a dose that results in a 10% reduction in the response relative to the control

---

Summary of Model Fitting Results

```
      AIC       BIC    logLik
 54.02910  56.70022 -24.01455

Coefficients:
      Value Std.Error
A 11.774107 0.4600004
m  0.986816 0.1223086

Correlation:
          A         m
A 1.0000000 0.7692694
m 0.7692694 1.0000000

Approximate 95% confidence intervals

 Coefficients:
      lower      est.     upper
A 10.838240 11.774107 12.790785
m  0.758799  0.986816  1.283351

 Residual standard error:
    lower      est.     upper
0.9013439 1.2102315 1.8418863

Degrees of freedom: 18 total; 16 residual
```



Goodness of Fit

The chi-squared goodness-of-fit values should be taken as general indications of fit only. P-values are likely to be inaccurate to some degree

Pearson Chi-Square Statistic: 2.564 with 1 degrees of freedom. P = 0.109

	dose	n	chei	Expected	sd	Exp.SD	X2 Resid.
1	0.00	6	11.45	11.774107	1.267	1.2311843	-0.6448243
2	0.25	6	9.72	9.199957	0.796	0.9744274	1.3072697
3	0.50	6	6.98	7.188589	0.756	0.7712158	-0.6625066

BMD Computation

BMD = 0.1068: BMDL = 0.08869

Potency Measures

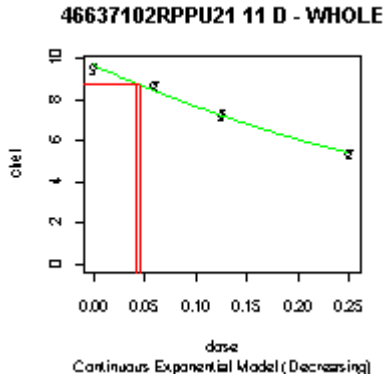
A unit dose (1 mg/kg) would result in 100*exp(-Potency)% of background activity

Potency: 0.9868
se: 0.1223
var=se^2: 0.01496
Per cent. of background at unit dose: 37
Per cent. of background at the highest dose: 61
ED50 (95% CI): 0.7024 (0.5509 , 0.8956)

ln(Potency) -0.01327
se[log(Potency)]: 0.1239
se[log(Potency)]^2: 0.0153

b. Pup, Repeated

```
                    DISULFOTON:11-D:BRAIN:F:WHOLE
                        Fri Jan 04 19:39:47 1980
                MRID: 46637102RPPU21   Guideline: NONGUIDELINE
                  Continuous Exponential Model (Decreasing)
                  Formula: chei = B + (A-B)*exp(-(m*dose)^g)

Variance Function: power


   The BMD corresponds to a dose that results in a 10% reduction in the
                        response relative to the control
    ------------------------------------------------------------------
                        Summary of Model Fitting Results

      AIC       BIC    logLik
25.736836 30.569590 -9.868418

Coefficients:
     Value Std.Error
A 9.700061 0.1054270
m 2.349013 0.0773280

Correlation:
          A         m
A 1.0000000 0.7582823
m 0.7582823 1.0000000

Approximate 95% confidence intervals

 Coefficients:
     lower     est.    upper
A 9.488376 9.700061 9.916468
m 2.197160 2.349013 2.511362

 Residual standard error:
    lower      est.     upper
0.3317666 0.4090422 0.5335702

Degrees of freedom: 37 total; 35 residual
    ------------------------------------------------------------------
                              Goodness of Fit
 The chi-squared goodness-of-fit values should be taken as general
indications of fit only.  P-values are likely to be inaccurate to some
degree

Pearson Chi-Square Statistic: 5.789 with 2 degrees of freedom.  P =
0.0553

   dose  n chei Expected    sd    Exp.SD  X2 Resid.
1 0.000  9 9.50 9.700061 0.372 0.4158100 -1.4434042
2 0.060 10 8.64 8.424898 0.236 0.3622483  1.8777542
3 0.125  9 7.22 7.231926 0.326 0.3119803 -0.1146848
```



```
4 0.250  9 5.36 5.391797 0.265 0.2340773 -0.4075226

    ------------------------------------------------------------------
                              BMD Computation

                      BMD = 0.04485:  BMDL = 0.04255

    ------------------------------------------------------------------
                              Potency Measures

A unit dose (1 mg/kg) would result in 100*exp(-Potency)% of background
activity

Potency: 2.349
se: 0.07733
var=se^2: 0.00598
Per cent. of background at unit dose: 9.5
Per cent. of background at the highest dose: 56
ED50 (95% CI): 0.2951 ( 0.2766 , 0.3147 )

ln(Potency) 0.854
se[log(Potency)]: 0.03292
se[log(Potency)]^2: 0.001084
```

DISULFOTON:11-D:BRAIN:M:WHOLE
Fri Jan 04 19:39:55 1980
MRID: 46637102RPPU21 Guideline: NONGUIDELINE
Continuous Exponential Model (Decreasing)
Formula: chei = B + (A-B)*exp(-(m*dose)^g)

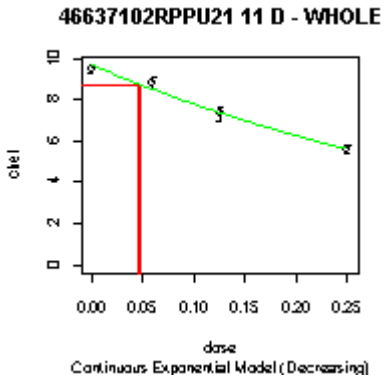
Variance Function: power

The BMD corresponds to a dose that results in a 10% reduction in the response relative to the control

---

Summary of Model Fitting Results

```
      AIC       BIC    logLik
 41.66038  46.65107 -17.83019

Coefficients:
     Value  Std.Error
A 9.690200 0.12045826
m 2.192024 0.08981002

Correlation:
          A         m
A 1.0000000 0.7540415
m 0.7540415 1.0000000

Approximate 95% confidence intervals

 Coefficients:
     lower     est.    upper
A 9.449177 9.690200 9.937372
m 2.017400 2.192024 2.381763

 Residual standard error:
    lower      est.     upper
0.3933414 0.4824713 0.6241960

Degrees of freedom: 39 total; 37 residual
```



Goodness of Fit

The chi-squared goodness-of-fit values should be taken as general indications of fit only. P-values are likely to be inaccurate to some degree

Pearson Chi-Square Statistic: 7.761 with 2 degrees of freedom. P = 0.0206

	dose	n	chei	Expected	sd	Exp.SD	X2 Resid.
1	0.000	10	9.47	9.690200	0.335	0.4917414	-1.4160588
2	0.060	10	8.81	8.495985	0.405	0.4323255	2.2968893
3	0.125	10	7.29	7.367748	0.455	0.3760317	-0.6538292
4	0.250	9	5.58	5.601918	0.203	0.2875492	-0.2286722

BMD Computation

BMD = 0.04807: BMDL = 0.04503

Potency Measures

A unit dose (1 mg/kg) would result in 100*exp(-Potency)% of background activity

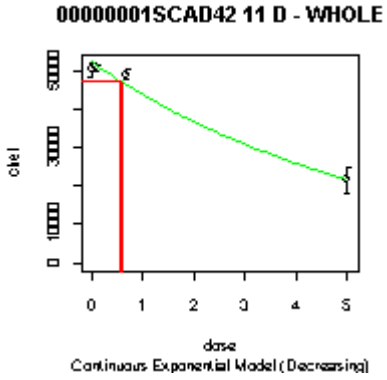
Potency: 2.192
se: 0.08981
var=se^2: 0.008066
Per cent. of background at unit dose: 11
Per cent. of background at the highest dose: 58
ED50 (95% CI): 0.3162 (0.2918 , 0.3427)

ln(Potency) 0.7848
se[log(Potency)]: 0.04097
se[log(Potency)]^2: 0.001679

8. Fosthiazate

a. Adult, Repeated

```
                Fosthiazate:11-D:BRAIN:F:WHOLE
                    Fri Jan 04 17:04:03 1980
          MRID: 00000001SCAD42   Guideline: NONGUIDELINE
            Continuous Exponential Model (Decreasing)
            Formula: chei = B + (A-B)*exp(-(m*dose)^g)

Variance Function: power


   The BMD corresponds to a dose that results in a 10% reduction in the
                    response relative to the control
    ------------------------------------------------------------------
                    Summary of Model Fitting Results

      AIC       BIC    logLik
 771.0335  776.0242 -382.5167

Coefficients:
         Value    Std.Error
A 5.231487e+04 1.146822e+03
m 1.764253e-01 8.763907e-03

Correlation:
          A         m
A 1.0000000 0.5728014
m 0.5728014 1.0000000

Approximate 95% confidence intervals

 Coefficients:
         lower         est.        upper
A 5.004204e+04 5.231487e+04 5.469093e+04
m 1.595323e-01 1.764253e-01 1.951070e-01

 Residual standard error:
   lower     est.    upper
4622.142 5669.505 7334.907

Degrees of freedom: 39 total; 37 residual
    ------------------------------------------------------------------
                            Goodness of Fit
 The chi-squared goodness-of-fit values should be taken as general
indications of fit only.  P-values are likely to be inaccurate to some
degree

Pearson Chi-Square Statistic: 3.973 with 2 degrees of freedom.  P =
0.137
```



	dose	n	chei	Expected	sd	Exp.SD	X2 Resid.
1	0.0	9	50227	52314.87	2570.2	5816.164	-1.0769337
2	0.1	10	50726	51400.00	1031.3	5718.097	-0.3727430
3	0.7	10	48882	46237.12	1780.8	5163.463	1.6198102
4	5.0	10	21476	21653.22	4545.2	2485.323	-0.2254954

BMD Computation

BMD = 0.5972: BMDL = 0.5521

Potency Measures

A unit dose (1 mg/kg) would result in 100*exp(-Potency)% of background activity

Potency: 0.1764
se: 0.008764
var=se^2: 7.681e-05
Per cent. of background at unit dose: 84
Per cent. of background at the highest dose: 41
ED50 (95% CI): 3.929 (3.564 , 4.331)

ln(Potency) -1.735
se[log(Potency)]: 0.04967
se[log(Potency)]^2: 0.002468

Fosthiazate:11-D:BRAIN:M:WHOLE
Fri Jan 04 17:04:12 1980
MRID: 00000001SCAD42 Guideline: NONGUIDELINE
Continuous Exponential Model (Decreasing)
Formula: chei = B + (A-B)*exp(-(m*dose)^g)

Variance Function: power

The BMD corresponds to a dose that results in a 10% reduction in the response relative to the control

---

Summary of Model Fitting Results

AIC	BIC	logLik
756.4962	761.5628	-375.2481

Coefficients:

	Value	Std.Error
A	5.069850e+04	6.164745e+02
m	5.587328e-02	4.823793e-03

Correlation:

	A	m
A	1.0000000	0.5736298
m	0.5736298	1.0000000

Approximate 95% confidence intervals

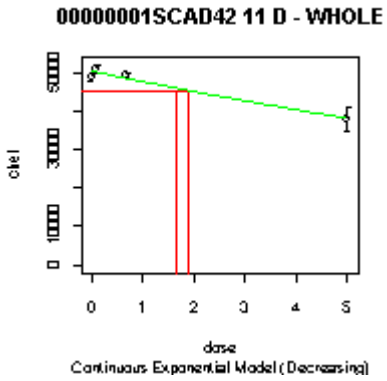
Coefficients:

	lower	est.	upper
A	4.946575e+04	5.069850e+04	5.196197e+04
m	4.691377e-02	5.587328e-02	6.654387e-02

Residual standard error:

lower	est.	upper
2635.439	3224.781	4156.027

Degrees of freedom: 40 total; 38 residual



Goodness of Fit

The chi-squared goodness-of-fit values should be taken as general indications of fit only. P-values are likely to be inaccurate to some degree

Pearson Chi-Square Statistic: 3.652 with 2 degrees of freedom. P = 0.161

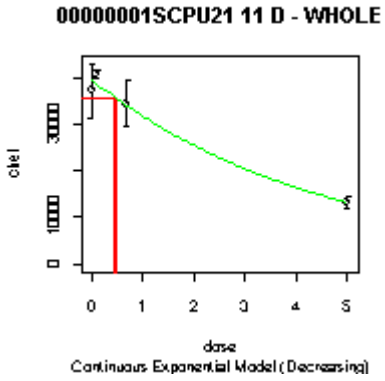
	dose	n	chei	Expected	sd	Exp.SD	X2 Resid.
1	0.0	10	49176	50698.50	1372.3	3191.493	-1.5085630
2	0.1	10	51198	50416.02	1783.8	3173.860	0.7791255
3	0.7	10	49595	48753.89	907.2	3070.090	0.8663646
4	5.0	10	38237	38341.39	4346.9	2419.294	-0.1364445

```
------------------------------------------------------------------
                        BMD Computation

                  BMD = 1.886:  BMDL = 1.651

------------------------------------------------------------------
                        Potency Measures

A unit dose (1 mg/kg) would result in 100*exp(-Potency)% of background
activity

Potency: 0.05587
se: 0.004824
var=se^2: 2.327e-05
Per cent. of background at unit dose: 95
Per cent. of background at the highest dose: 76
ED50 (95% CI): 12.41 ( 10.47 , 14.69 )

ln(Potency) -2.885
se[log(Potency)]: 0.08633
```

se[log(Potency)]^2: 0.007454

b. Pup, Repeated

```
                    Fosthiazate:11-D:BRAIN:F:WHOLE
                        Fri Jan 04 17:04:21 1980
                MRID: 00000001SCPU21   Guideline: NONGUIDELINE
                  Continuous Exponential Model (Decreasing)
                  Formula: chei = B + (A-B)*exp(-(m*dose)^g)

Variance Function: power


   The BMD corresponds to a dose that results in a 10% reduction in the
                    response relative to the control
    ------------------------------------------------------------------
                    Summary of Model Fitting Results

      AIC       BIC    logLik
 794.2296  799.2963 -394.1148

Coefficients:
         Value    Std.Error
A 3.974383e+04 1.250093e+03
m 2.210278e-01 1.263111e-02

Correlation:
          A         m
A 1.0000000 0.5687707
m 0.5687707 1.0000000

Approximate 95% confidence intervals

 Coefficients:
         lower         est.        upper
A 3.729203e+04 3.974383e+04 4.235682e+04
m 1.968811e-01 2.210278e-01 2.481359e-01

 Residual standard error:
   lower     est.    upper
5457.450 6677.856 8606.275

Degrees of freedom: 40 total; 38 residual
    ------------------------------------------------------------------
                              Goodness of Fit
 The chi-squared goodness-of-fit values should be taken as general
indications of fit only.  P-values are likely to be inaccurate to some
degree

Pearson Chi-Square Statistic: 2.562 with 2 degrees of freedom.  P =
0.278

  dose  n  chei Expected     sd   Exp.SD   X2 Resid.
1  0.0 10 37284 39743.83 8312.6 6465.951 -1.20301754
2  0.1 10 40936 38875.01 1081.5 6327.118  1.03007554
3  0.7 10 34444 34046.77 6956.5 5554.526  0.22615114
```



```
4  5.0 10 13125 13161.76 1810.5 2184.277 -0.05321862

    ------------------------------------------------------------------
                              BMD Computation

                      BMD = 0.4767:  BMDL = 0.4357

    ------------------------------------------------------------------
                              Potency Measures

A unit dose (1 mg/kg) would result in 100*exp(-Potency)% of background
activity

Potency: 0.221
se: 0.01263
var=se^2: 0.0001595
Per cent. of background at unit dose: 80
Per cent. of background at the highest dose: 33
ED50 (95% CI): 3.136 ( 2.804 , 3.508 )

ln(Potency) -1.509
se[log(Potency)]: 0.05715
```
se[log(Potency)]^2: 0.003266

Fosthiazate:11-D:BRAIN:M:WHOLE
Fri Jan 04 17:04:28 1980
MRID: 00000001SCPU21 Guideline: NONGUIDELINE
Continuous Exponential Model (Decreasing)
Formula: chei = B + (A-B)*exp(-(m*dose)^g)

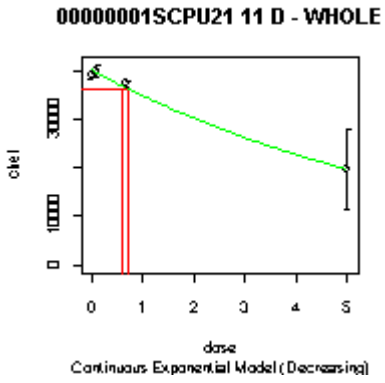
Variance Function: power

The BMD corresponds to a dose that results in a 10% reduction in the response relative to the control

---

Summary of Model Fitting Results

```
      AIC       BIC    logLik
 849.4277  854.4943 -421.7138

Coefficients:
         Value    Std.Error
A 4.039893e+04 2.229497e+03
m 1.428993e-01 2.204119e-02

Correlation:
          A         m
A 1.0000000 0.5709342
m 0.5709342 1.0000000

Approximate 95% confidence intervals

 Coefficients:
         lower         est.        upper
A 3.612853e+04 4.039893e+04 4.517408e+04
m 1.045737e-01 1.428993e-01 1.952711e-01

 Residual standard error:
    lower      est.     upper
 9377.115 11474.044 14787.498

Degrees of freedom: 40 total; 38 residual
```



Goodness of Fit

The chi-squared goodness-of-fit values should be taken as general indications of fit only. P-values are likely to be inaccurate to some degree

Pearson Chi-Square Statistic: 0.2129 with 2 degrees of freedom. P = 0.899

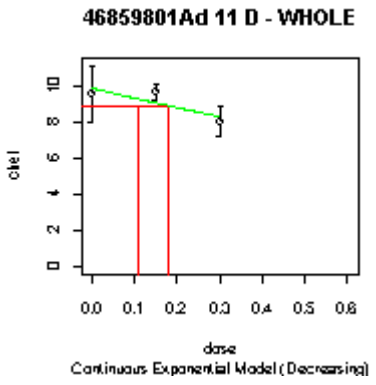
	dose	n	chei	Expected	sd	Exp.SD	X2 Resid.
1	0.0	10	39177	40398.93	1109.0	11536.40	-0.33494641
2	0.1	10	40093	39825.74	2031.0	11375.46	0.07429724
3	0.7	10	37563	36553.38	825.1	10455.89	0.30534876
4	5.0	10	19692	19772.79	11643.7	5714.83	-0.04470237

```
-------------------------------------------------------------------
                          BMD Computation

                  BMD = 0.7373:  BMDL = 0.5881

-------------------------------------------------------------------
                          Potency Measures

A unit dose (1 mg/kg) would result in 100*exp(-Potency)% of background
activity

Potency: 0.1429
se: 0.02204
var=se^2: 0.0004858
Per cent. of background at unit dose: 87
Per cent. of background at the highest dose: 49
ED50 (95% CI): 4.851 ( 3.585 , 6.563 )

ln(Potency) -1.946
se[log(Potency)]: 0.1542
se[log(Potency)]^2: 0.02379
```

9. Methamidophos

a. Adult, Repeated

```
                Methamidophos:11-D:BRAIN:F:WHOLE
                     Sun Feb 17 20:36:39 2002
           MRID: 46859801Ad   Guideline: NONGUIDELINE
           Continuous Exponential Model (Decreasing)
           Formula: chei = B + (A-B)*exp(-(m*dose)^g)

Variance Function: power

Highest 1 doses dropped from data set.


   The BMD corresponds to a dose that results in a 10% reduction in the
                    response relative to the control
    ------------------------------------------------------------------
                    Summary of Model Fitting Results

      AIC       BIC    logLik
 56.17302  58.84414 -25.08651

Coefficients:
      Value Std.Error
A 9.8844932 0.4189034
m 0.5824907 0.2197488

Correlation:
          A         m
A 1.0000000 0.7724789
m 0.7724789 1.0000000

Approximate 95% confidence intervals

 Coefficients:
      lower      est.     upper
A 9.0351806 9.8844932 10.813642
m 0.2617955 0.5824907  1.296032

 Residual standard error:
    lower      est.     upper
0.8195475 1.1004037 1.6747363

Degrees of freedom: 18 total; 16 residual
    ------------------------------------------------------------------
                             Goodness of Fit
 The chi-squared goodness-of-fit values should be taken as general
indications of fit only.  P-values are likely to be inaccurate to some
degree

Pearson Chi-Square Statistic: 2.855 with 1 degrees of freedom.  P =
0.0911
```



```
  dose n chei Expected    sd    Exp.SD  X2 Resid.
1 0.00 6 9.57 9.884493 1.512 1.1228915 -0.6860395
2 0.15 6 9.64 9.057504 0.442 1.0342205  1.3796071
3 0.30 6 8.03 8.299705 0.758 0.9525516 -0.6935475

    ------------------------------------------------------------------
                            BMD Computation

                      BMD = 0.1809:  BMDL = 0.1116

    ------------------------------------------------------------------
                            Potency Measures

A unit dose (1 mg/kg) would result in 100*exp(-Potency)% of background
activity

Potency: 0.5825
se: 0.2197
var=se^2: 0.04829
Per cent. of background at unit dose: 56
Per cent. of background at the highest dose: 84
ED50 (95% CI): 1.19 ( 0.5681 , 2.493 )

ln(Potency) -0.5404
se[log(Potency)]: 0.3773
se[log(Potency)]^2: 0.1423
```

Methamidophos:11-D:BRAIN:M:WHOLE
Sun Feb 17 20:37:16 2002
MRID: 46859801Ad Guideline: NONGUIDELINE
Continuous Exponential Model (Decreasing)
Formula: chei = B + (A-B)*exp(-(m*dose)^g)

Variance Function: power

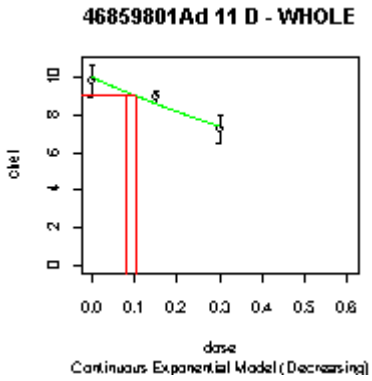
Highest 1 doses dropped from data set.

The BMD corresponds to a dose that results in a 10% reduction in the response relative to the control

---

Summary of Model Fitting Results

```
      AIC       BIC    logLik
 41.26049  43.93160 -17.63024

Coefficients:
      Value Std.Error
A 10.039986 0.2952989
m  1.019360 0.1526541

Correlation:
          A         m
A 1.0000000 0.7719894
m 0.7719894 1.0000000

Approximate 95% confidence intervals

 Coefficients:
      lower      est.     upper
A 9.4330967 10.039986 10.685919
m 0.7420852  1.019360  1.400236

 Residual standard error:
    lower      est.     upper
0.5802877 0.7791504 1.1858116

Degrees of freedom: 18 total; 16 residual
```



Goodness of Fit

The chi-squared goodness-of-fit values should be taken as general indications of fit only. P-values are likely to be inaccurate to some degree

Pearson Chi-Square Statistic: 2.533 with 1 degrees of freedom. P = 0.112

	dose	n	chei	Expected	sd	Exp.SD	X2 Resid.
1	0.00	6	9.83	10.039986	0.854	0.7913788	-0.6499513
2	0.15	6	8.98	8.616437	0.307	0.6834587	1.3029945
3	0.30	6	7.24	7.394731	0.680	0.5902557	-0.6421149

BMD Computation

BMD = 0.1034: BMDL = 0.08293

Potency Measures

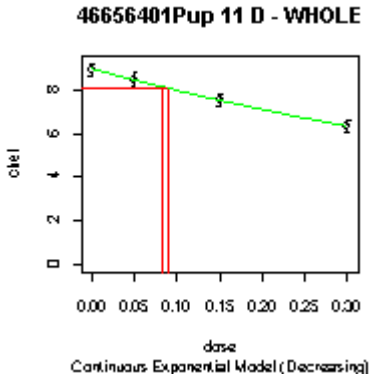
A unit dose (1 mg/kg) would result in 100*exp(-Potency)% of background activity

Potency: 1.019
se: 0.1527
var=se^2: 0.0233
Per cent. of background at unit dose: 36
Per cent. of background at the highest dose: 74
ED50 (95% CI): 0.68 (0.507 , 0.912)

ln(Potency) 0.01917
se[log(Potency)]: 0.1498
se[log(Potency)]^2: 0.02243

b. Pup, Repeated

```
                    Methamidophos:11-D:BRAIN:F:WHOLE
                         Sun Feb 17 20:33:19 2002
                  MRID: 46656401Pup   Guideline: NONGUIDELINE
                   Continuous Exponential Model (Decreasing)
                   Formula: chei = B + (A-B)*exp(-(m*dose)^g)

Variance Function: power


   The BMD corresponds to a dose that results in a 10% reduction in the
                       response relative to the control
    ------------------------------------------------------------------
                       Summary of Model Fitting Results

      AIC       BIC    logLik
 41.41324  46.47987 -17.70662

Coefficients:
     Value  Std.Error
A 8.987019 0.10454000
m 1.158569 0.06860376

Correlation:
          A         m
A 1.0000000 0.7372098
m 0.7372098 1.0000000

Approximate 95% confidence intervals

 Coefficients:
     lower     est.    upper
A 8.777861 8.987019 9.201161
m 1.027689 1.158569 1.306117

 Residual standard error:
    lower      est.     upper
0.3643953 0.4458821 0.5746431

Degrees of freedom: 40 total; 38 residual
    ------------------------------------------------------------------
                              Goodness of Fit
 The chi-squared goodness-of-fit values should be taken as general
indications of fit only.  P-values are likely to be inaccurate to some
degree

Pearson Chi-Square Statistic: 0.07411 with 2 degrees of freedom.  P =
0.964
```



	dose	n	chei	Expected	sd	Exp.SD	X2 Resid.
1	0.00	10	8.97	8.987019	0.407	0.4467280	-0.12047342
2	0.05	10	8.51	8.481207	0.415	0.4215851	0.21597626
3	0.15	10	7.54	7.553385	0.349	0.3754648	-0.11273291
4	0.30	10	6.35	6.348448	0.393	0.3155696	0.01554928

BMD Computation

BMD = 0.09094: BMDL = 0.08287

Potency Measures

A unit dose (1 mg/kg) would result in 100*exp(-Potency)% of background activity

Potency: 1.159
se: 0.0686
var=se^2: 0.004706
Per cent. of background at unit dose: 31
Per cent. of background at the highest dose: 71
ED50 (95% CI): 0.5983 (0.5327 , 0.6719)

ln(Potency) 0.1472
se[log(Potency)]: 0.05921
se[log(Potency)]^2: 0.003506

Methamidophos:11-D:BRAIN:M:WHOLE
Sun Feb 17 20:33:49 2002
MRID: 46656401Pup Guideline: NONGUIDELINE
Continuous Exponential Model (Decreasing)
Formula: chei = B + (A-B)*exp(-(m*dose)^g)

Variance Function: power

The BMD corresponds to a dose that results in a 10% reduction in the response relative to the control

---

Summary of Model Fitting Results

AIC	BIC	logLik
39.39394	46.14946	-15.69697

Coefficients:

	Value	Std.Error
A	9.024311	0.1247331
B	4.263469	1.5687256
m	2.759075	1.3908508

Correlation:

	A	B	m
A	1.0000000	0.5038750	0.5700879
B	0.5038750	1.0000000	0.9925059
m	0.5700879	0.9925059	1.0000000

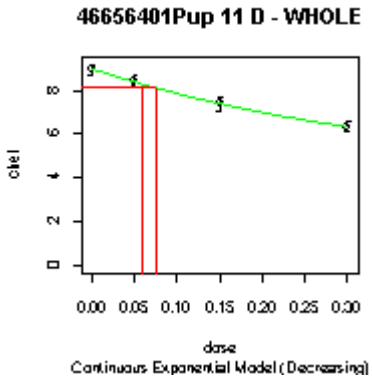
Approximate 95% confidence intervals

Coefficients:

	lower	est.	upper
A	8.7750842	9.024311	9.280617
B	2.0229445	4.263469	8.985500
m	0.9935122	2.759075	7.662206

Residual standard error:

lower	est.	upper
0.3532281	0.4332684	0.5605399



Degrees of freedom: 40 total; 37 residual

Goodness of Fit

The chi-squared goodness-of-fit values should be taken as general indications of fit only. P-values are likely to be inaccurate to some degree

Pearson Chi-Square Statistic: 0.3533 with 1 degrees of freedom. P = 0.552

	dose	n	chei	Expected	sd	Exp.SD	X2 Resid.
1	0.00	10	8.99	9.024311	0.328	0.4346546	-0.24962762
2	0.05	10	8.47	8.410824	0.315	0.4054724	0.46151099
3	0.15	10	7.38	7.410827	0.479	0.3574913	-0.27268752
4	0.30	10	6.35	6.344164	0.321	0.3055677	0.06039276

BMD Computation

BMD = 0.07617: BMDL = 0.06053

Potency Measures

A unit dose (1 mg/kg) would result in 100*exp(-Potency)% of background activity

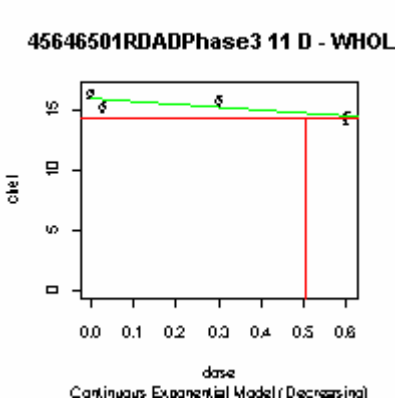
Potency: 2.759
se: 1.391
var=se^2: 1.934
Per cent. of background at unit dose: 6.3
Per cent. of background at the highest dose: 44
ED50 (95% CI): 0.2512 (0.09353 , 0.6748)

ln(Potency) 1.015
se[log(Potency)]: 0.5041
se[log(Potency)]^2: 0.2541

10. Methyl Parathion

a. Adult, Repeated

```
                METHYL PARATHION:11-D:BRAIN:F:WHOLE
                      Fri Jan 04 14:23:40 1980
            MRID: 45646501RDADPhase3   Guideline: NONGUIDELINE
                Continuous Exponential Model (Decreasing)
                Formula: chei = B + (A-B)*exp(-(m*dose)^g)

Variance Function: power


   The BMD corresponds to a dose that results in a 10% reduction in the
                    response relative to the control
    ------------------------------------------------------------------
                    Summary of Model Fitting Results

      AIC       BIC    logLik
170.68648 177.16313 -82.34324

Coefficients:
       Value  Std.Error
A 15.9491003 0.15998987
m  0.1601876 0.02990362

Correlation:
          A         m
A 1.0000000 0.6920998
m 0.6920998 1.0000000

Approximate 95% confidence intervals

 Coefficients:
       lower       est.      upper
A 15.6324703 15.9491003 16.2721435
m  0.1102974  0.1601876  0.2326444

 Residual standard error:
    lower      est.     upper
0.8052404 0.9464613 1.1482162

Degrees of freedom: 64 total; 62 residual
    ------------------------------------------------------------------
                              Goodness of Fit
 The chi-squared goodness-of-fit values should be taken as general
indications of fit only.  P-values are likely to be inaccurate to some
degree

Pearson Chi-Square Statistic: 17.06 with 2 degrees of freedom.  P =
0.000197
```



	dose	n	chei	Expected	sd	Exp.SD	X2 Resid.
1	0.00	16	16.34	15.94910	0.684	0.9232395	1.6936005
2	0.03	16	15.20	15.87264	0.746	0.9188915	-2.9280442
3	0.30	16	15.68	15.20077	0.671	0.8806700	2.1766570
4	0.60	16	14.29	14.48755	0.923	0.8400633	-0.9406575

BMD Computation

BMD = 0.6577: BMDL = 0.5032

Potency Measures

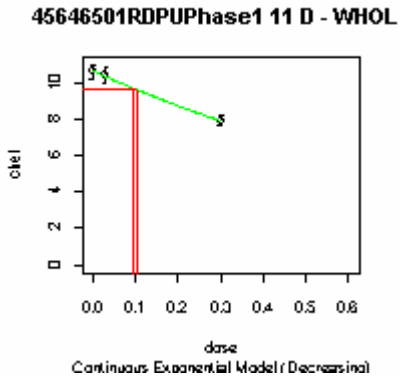
A unit dose (1 mg/kg) would result in 100*exp(-Potency)% of background activity

Potency: 0.1602
se: 0.0299
var=se^2: 0.0008942
Per cent. of background at unit dose: 85
Per cent. of background at the highest dose: 91
ED50 (95% CI): 4.327 (3.001 , 6.239)

ln(Potency) -1.831
se[log(Potency)]: 0.1867
se[log(Potency)]^2: 0.03485

b. Pup, Repeated

```
                METHYL PARATHION:11-D:BRAIN:F:WHOLE
                       Fri Jan 04 14:23:59 1980
            MRID: 45646501RDPUPhase1   Guideline: NONGUIDELINE
                Continuous Exponential Model (Decreasing)
                Formula: chei = B + (A-B)*exp(-(m*dose)^g)

Variance Function: power

Highest 1 doses dropped from data set.


   The BMD corresponds to a dose that results in a 10% reduction in the
                       response relative to the control
    ------------------------------------------------------------------
                       Summary of Model Fitting Results

      AIC       BIC    logLik
105.54891 111.16251 -49.77445

Coefficients:
       Value  Std.Error
A 10.6610185 0.14489339
m  0.9980264 0.07809508

Correlation:
          A         m
A 1.0000000 0.6318274
m 0.6318274 1.0000000

Approximate 95% confidence intervals

 Coefficients:
      lower       est.    upper
A 10.373317 10.6610185 10.95670
m  0.852584  0.9980264  1.16828

 Residual standard error:
    lower      est.     upper
0.6446817 0.7758137 0.9744110

Degrees of freedom: 48 total; 46 residual
    ------------------------------------------------------------------
                              Goodness of Fit
 The chi-squared goodness-of-fit values should be taken as general
indications of fit only.  P-values are likely to be inaccurate to some
degree

Pearson Chi-Square Statistic: 0.05715 with 1 degrees of freedom.  P =
0.811


  dose  n  chei  Expected    sd    Exp.SD   X2 Resid.
```



```
1 0.00 16 10.63 10.661018 0.728 0.7779939 -0.15947931
2 0.03 16 10.38 10.346550 0.857 0.7550719  0.17719987
3 0.30 16  7.90  7.902554 0.547 0.5768957 -0.01771025

    ------------------------------------------------------------------
                            BMD Computation

                      BMD = 0.1056:  BMDL = 0.09353

    ------------------------------------------------------------------
                            Potency Measures

A unit dose (1 mg/kg) would result in 100*exp(-Potency)% of background
activity

Potency: 0.998
se: 0.0781
var=se^2: 0.006099
Per cent. of background at unit dose: 37
Per cent. of background at the highest dose: 74
ED50 (95% CI): 0.6945 ( 0.5958 , 0.8096 )

ln(Potency) -0.001976
se[log(Potency)]: 0.07825
se[log(Potency)]^2: 0.006123
```

METHYL PARATHION:11-D:BRAIN:M:WHOLE
Fri Jan 04 14:24:09 1980
MRID: 45646501RDPUPhase1 Guideline: NONGUIDELINE
Continuous Exponential Model (Decreasing)
Formula: chei = B + (A-B)*exp(-(m*dose)^g)

Variance Function: power

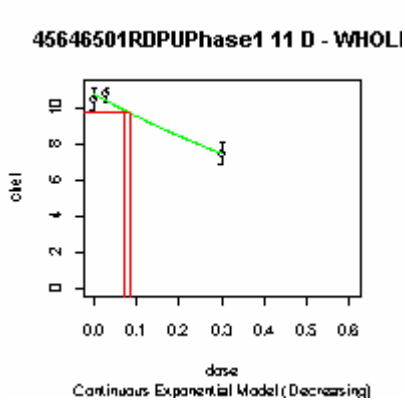
Highest 1 doses dropped from data set.

The BMD corresponds to a dose that results in a 10% reduction in the response relative to the control

---

Summary of Model Fitting Results

```
      AIC       BIC    logLik
151.25461 156.86822 -72.62731

Coefficients:
      Value Std.Error
A 10.809039 0.2388483
m  1.225511 0.1272956

Correlation:
          A         m
A 1.0000000 0.6305977
m 0.6305977 1.0000000

Approximate 95% confidence intervals

 Coefficients:
       lower      est.     upper
A 10.3387980 10.809039 11.300668
m  0.9942922  1.225511  1.510500

 Residual standard error:
   lower     est.    upper
1.061047 1.276870 1.603730

Degrees of freedom: 48 total; 46 residual
```



Goodness of Fit

The chi-squared goodness-of-fit values should be taken as general indications of fit only. P-values are likely to be inaccurate to some degree

Pearson Chi-Square Statistic: 2.088 with 1 degrees of freedom. P = 0.148

	dose	n	chei	Expected	sd	Exp.SD	X2 Resid.
1	0.00	16	10.50	10.809039	1.064	1.2822245	-0.9640720
2	0.03	16	10.75	10.418858	0.803	1.2364853	1.0712374
3	0.30	16	7.46	7.483715	1.202	0.8916881	-0.1063828

BMD Computation

BMD = 0.08597: BMDL = 0.07343

Potency Measures

A unit dose (1 mg/kg) would result in 100*exp(-Potency)% of background activity

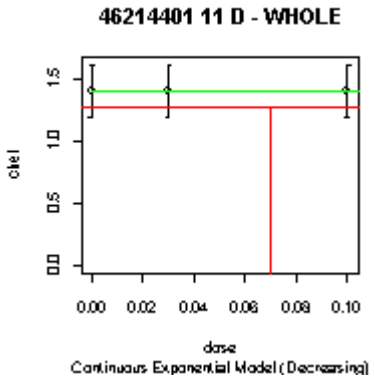
Potency: 1.226
se: 0.1273
var=se^2: 0.0162
Per cent. of background at unit dose: 29
Per cent. of background at the highest dose: 69
ED50 (95% CI): 0.5656 (0.4614 , 0.6933)

ln(Potency) 0.2034
se[log(Potency)]: 0.1039
se[log(Potency)]^2: 0.01079

11. Phorate

a. Pup, Repeated

```
                    Phorate:11-D:BRAIN:F:WHOLE
                      Fri Jan 04 20:39:04 1980
                MRID: 46214401   Guideline: NONGUIDELINE
               Continuous Exponential Model (Decreasing)
               Formula: chei = B + (A-B)*exp(-(m*dose)^g)

Variance Function: power


   The BMD corresponds to a dose that results in a 10% reduction in the
                    response relative to the control
    ------------------------------------------------------------------
                    Summary of Model Fitting Results

      AIC       BIC    logLik
15.737128 19.940720 -4.868564

Coefficients:
         Value  Std.Error
A 1.400000e+00 0.07737654
m 2.624270e-05 0.91691413

Correlation:
          A         m
A 1.0000000 0.7189016
m 0.7189016 1.0000000

Approximate 95% confidence intervals

 Coefficients:
     lower         est.    upper
A 1.250144 1.400000e+00 1.567819
m 0.000000 2.624270e-05      Inf

 Residual standard error:
    lower      est.     upper
0.2337841 0.2945945 0.3984248

Degrees of freedom: 30 total; 28 residual
    ------------------------------------------------------------------
                              Goodness of Fit
 The chi-squared goodness-of-fit values should be taken as general
indications of fit only.  P-values are likely to be inaccurate to some
degree

Pearson Chi-Square Statistic: 1.695e-09 with 1 degrees of freedom.  P
= 1
```



```
  dose  n chei Expected  sd    Exp.SD    X2 Resid.
1 0.00 10  1.4 1.400000 0.3 0.2945945 3.557377e-11
2 0.03 10  1.4 1.399999 0.3 0.2945943 1.183136e-05
3 0.10 10  1.4 1.399996 0.3 0.2945937 3.943781e-05

    ------------------------------------------------------------------
                            BMD Computation

                      BMD = 4015:  BMDL = 0.06986

    ------------------------------------------------------------------
                            Potency Measures

A unit dose (1 mg/kg) would result in 100*exp(-Potency)% of background
activity

Potency: 2.624e-05
se: 0.9169
var=se^2: 0.8407
Per cent. of background at unit dose: 100
Per cent. of background at the highest dose: 100
ED50 (95% CI): 26410 ( 0 , Inf )

ln(Potency) -10.55
se[log(Potency)]: 34940
se[log(Potency)]^2: 1.221e+09
```

Phorate:11-D:BRAIN:M:WHOLE
Fri Jan 04 20:39:14 1980
MRID: 46214401 Guideline: NONGUIDELINE
Continuous Exponential Model (Decreasing)
Formula: chei = B + (A-B)*exp(-(m*dose)^g)

Variance Function: power

The BMD corresponds to a dose that results in a 10% reduction in the response relative to the control

---

Summary of Model Fitting Results

AIC	BIC	logLik
-15.42306	-11.21946	10.71153

Coefficients:

	Value	Std.Error
A	1.398910	0.05109735
m	2.407170	0.60590437

Correlation:

	A	m
A	1.0000000	0.7189526
m	0.7189526	1.0000000

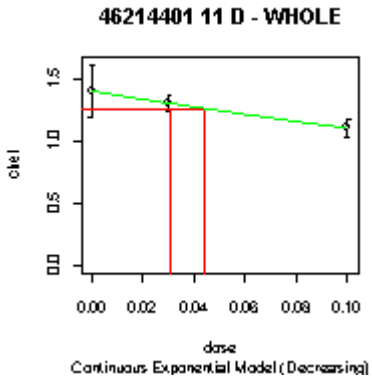
Approximate 95% confidence intervals

Coefficients:

	lower	est.	upper
A	1.298061	1.398910	1.507593
m	1.437422	2.407170	4.031154

Residual standard error:

lower	est.	upper
0.1544947	0.1946809	0.2632965



Degrees of freedom: 30 total; 28 residual

Goodness of Fit

The chi-squared goodness-of-fit values should be taken as general indications of fit only. P-values are likely to be inaccurate to some degree

Pearson Chi-Square Statistic: 0.001013 with 1 degrees of freedom. P = 0.975

	dose	n	chei	Expected	sd	Exp.SD	X2 Resid.
1	0.00	10	1.4	1.398910	0.3	0.1945472	0.017720948
2	0.03	10	1.3	1.301449	0.1	0.1809805	-0.025315000
3	0.10	10	1.1	1.099633	0.1	0.1528906	0.007597111

BMD Computation

BMD = 0.04377: BMDL = 0.03095

Potency Measures

A unit dose (1 mg/kg) would result in 100*exp(-Potency)% of background activity

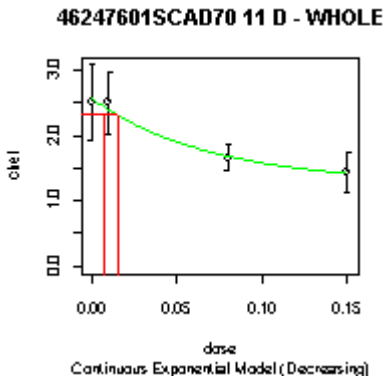
Potency: 2.407
se: 0.6059
var=se^2: 0.3671
Per cent. of background at unit dose: 9
Per cent. of background at the highest dose: 79
ED50 (95% CI): 0.288 (0.1758 , 0.4716)

ln(Potency) 0.8785
se[log(Potency)]: 0.2517
se[log(Potency)]^2: 0.06336

12. Terbufos

a. Adult, Repeated

```
                    Terbufos:11-D:BRAIN:F:WHOLE
                       Fri Jan 04 18:16:53 1980
              MRID: 46247601SCAD70   Guideline: NONGUIDELINE
                Continuous Exponential Model (Decreasing)
                Formula: chei = B + (A-B)*exp(-(m*dose)^g)

Variance Function: power


   The BMD corresponds to a dose that results in a 10% reduction in the
                    response relative to the control
    ------------------------------------------------------------------
                    Summary of Model Fitting Results

      AIC       BIC    logLik
143.64430 152.27983 -67.82215

Coefficients:
      Value  Std.Error
A  2.579956  0.1889585
B  1.271775  0.3970392
m 14.425263 12.2358396

Correlation:
          A         B         m
A 1.0000000 0.3010440 0.4260414
B 0.3010440 1.0000000 0.9450704
m 0.4260414 0.9450704 1.0000000

Approximate 95% confidence intervals

 Coefficients:
      lower      est.     upper
A 2.2284758  2.579956  2.986872
B 0.6812303  1.271775  2.374251
m 2.6454847 14.425263 78.657875

 Residual standard error:
    lower      est.     upper
0.7738684 0.9106888 1.1067344

Degrees of freedom: 64 total; 61 residual
    ------------------------------------------------------------------
                            Goodness of Fit
 The chi-squared goodness-of-fit values should be taken as general
indications of fit only.  P-values are likely to be inaccurate to some
degree

Pearson Chi-Square Statistic: 0.3361 with 1 degrees of freedom.  P =
```



0.562

	dose	n	chei	Expected	sd	Exp.SD	X2 Resid.
1	0.00	16	2.50	2.579956	1.10	0.9357818	-0.34177108
2	0.01	16	2.50	2.404227	0.91	0.8769715	0.43683705
3	0.08	16	1.66	1.684331	0.37	0.6202664	-0.15690602
4	0.15	16	1.43	1.422070	0.57	0.5139694	0.06171211

BMD Computation

BMD = 0.01523: BMDL = 0.007784

Potency Measures

A unit dose (1 mg/kg) would result in 100*exp(-Potency)% of background activity

Potency: 14.43
se: 12.24
var=se^2: 149.7
Per cent. of background at unit dose: 5.4e-05
Per cent. of background at the highest dose: 11
ED50 (95% CI): 0.04805 (0.009113 , 0.2534)

ln(Potency) 2.669
se[log(Potency)]: 0.8482
se[log(Potency)]^2: 0.7195

Terbufos:11-D:BRAIN:M:WHOLE
Fri Jan 04 18:17:02 1980
MRID: 46247601SCAD70 Guideline: NONGUIDELINE
Continuous Exponential Model (Decreasing)
Formula: chei = B + (A-B)*exp(-(m*dose)^g)

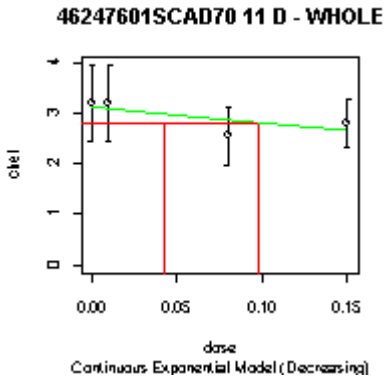
Variance Function: power

The BMD corresponds to a dose that results in a 10% reduction in the response relative to the control

---

Summary of Model Fitting Results

```
      AIC       BIC    logLik
 209.3039  215.7805 -101.6519

Coefficients:
     Value Std.Error
A 3.144962  0.227199
m 1.075126  0.842295

Correlation:
          A         m
A 1.0000000 0.7079674
m 0.7079674 1.0000000

Approximate 95% confidence intervals

 Coefficients:
      lower     est.    upper
A 2.7220671 3.144962 3.633556
m 0.2245551 1.075126 5.147489

 Residual standard error:
   lower     est.    upper
1.118651 1.314837 1.595117

Degrees of freedom: 64 total; 62 residual
```



Goodness of Fit

The chi-squared goodness-of-fit values should be taken as general indications of fit only. P-values are likely to be inaccurate to some degree

Pearson Chi-Square Statistic: 1.7 with 2 degrees of freedom. P = 0.428

	dose	n	chei	Expected	sd	Exp.SD	X2 Resid.
1	0.00	16	3.22	3.144962	1.46	1.291322	0.2324390
2	0.01	16	3.21	3.111330	1.42	1.276255	0.3092472
3	0.08	16	2.56	2.885770	1.06	1.175595	-1.1084417
4	0.15	16	2.83	2.676561	0.90	1.082874	0.5667836

BMD Computation

BMD = 0.098: BMDL = 0.04282

Potency Measures

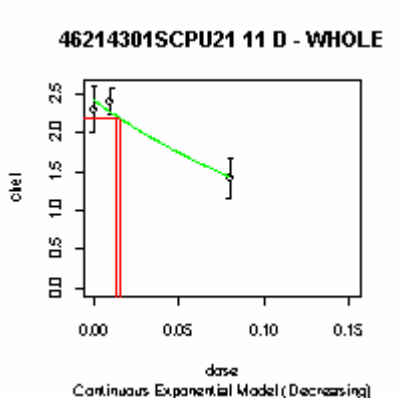
A unit dose (1 mg/kg) would result in 100*exp(-Potency)% of background activity

Potency: 1.075
se: 0.8423
var=se^2: 0.7095
Per cent. of background at unit dose: 34
Per cent. of background at the highest dose: 85
ED50 (95% CI): 0.6447 (0.1388 , 2.994)

ln(Potency) 0.07244
se[log(Potency)]: 0.7834
se[log(Potency)]^2: 0.6138

b. Pup, Repeated

```
                    Terbufos:11-D:BRAIN:F:WHOLE
                       Fri Jan 04 18:15:43 1980
              MRID: 46214301SCPU21   Guideline: NONGUIDELINE
                Continuous Exponential Model (Decreasing)
                Formula: chei = B + (A-B)*exp(-(m*dose)^g)

Variance Function: power

Highest 1 doses dropped from data set.


   The BMD corresponds to a dose that results in a 10% reduction in the
                    response relative to the control
    ------------------------------------------------------------------
                    Summary of Model Fitting Results

      AIC       BIC    logLik
 31.15934  35.36293 -12.57967

Coefficients:
     Value Std.Error
A 2.427871 0.1103401
m 6.606930 0.9860690

Correlation:
          A         m
A 1.0000000 0.6399046
m 0.6399046 1.0000000

Approximate 95% confidence intervals

 Coefficients:
     lower     est.    upper
A 2.212051 2.427871 2.664747
m 4.866617 6.606930 8.969583

 Residual standard error:
    lower      est.     upper
0.3652663 0.4602769 0.6225023

Degrees of freedom: 30 total; 28 residual
    ------------------------------------------------------------------
                              Goodness of Fit
 The chi-squared goodness-of-fit values should be taken as general
indications of fit only.  P-values are likely to be inaccurate to some
degree

Pearson Chi-Square Statistic: 1.79 with 1 degrees of freedom.  P =
0.181
```



	dose	n	chei	Expected	sd	Exp.SD	X2 Resid.
1	0.00	10	2.30	2.427871	0.41	0.4616504	-0.8759065
2	0.01	10	2.41	2.272647	0.25	0.4330055	1.0030998
3	0.08	10	1.42	1.431124	0.37	0.2765380	-0.1272065

BMD Computation

BMD = 0.01595: BMDL = 0.0128

Potency Measures

A unit dose (1 mg/kg) would result in 100*exp(-Potency)% of background activity

Potency: 6.607
se: 0.9861
var=se^2: 0.9723
Per cent. of background at unit dose: 0.14
Per cent. of background at the highest dose: 59
ED50 (95% CI): 0.1049 (0.0783 , 0.1406)

ln(Potency) 1.888
se[log(Potency)]: 0.1492
se[log(Potency)]^2: 0.02227

Terbufos:11-D:BRAIN:M:WHOLE
Fri Jan 04 18:15:54 1980
MRID: 46214301SCPU21 Guideline: NONGUIDELINE
Continuous Exponential Model (Decreasing)
Formula: chei = B + (A-B)*exp(-(m*dose)^g)

Variance Function: power

Highest 1 doses dropped from data set.

The BMD corresponds to a dose that results in a 10% reduction in the response relative to the control

---

Summary of Model Fitting Results

AIC	BIC	logLik
22.48412	26.68771	-8.24206

Coefficients:

	Value	Std.Error
A	2.367231	0.09659283
m	6.892402	0.88022711

Correlation:

	A	m
A	1.0000000	0.6425834
m	0.6425834	1.0000000

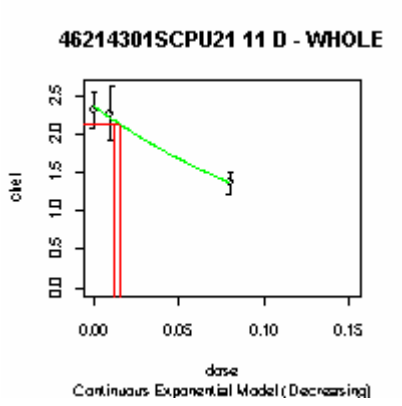
Approximate 95% confidence intervals

Coefficients:

	lower	est.	upper
A	2.177413	2.367231	2.573597
m	5.305893	6.892402	8.953292

Residual standard error:

lower	est.	upper
0.3150565	0.3970068	0.5369326



Degrees of freedom: 30 total; 28 residual

Goodness of Fit

The chi-squared goodness-of-fit values should be taken as general indications of fit only. P-values are likely to be inaccurate to some degree

Pearson Chi-Square Statistic: 0.3174 with 1 degrees of freedom. P = 0.573

	dose	n	chei	Expected	sd	Exp.SD	X2 Resid.
1	0.00	10	2.32	2.367231	0.33	0.4043590	-0.36937097
2	0.01	10	2.26	2.209568	0.49	0.3777446	0.42219003
3	0.08	10	1.36	1.363874	0.20	0.2345395	-0.05222699

```
-----------------------------------------------------------------
                        BMD Computation

                BMD = 0.01529:  BMDL = 0.01263

-----------------------------------------------------------------
                        Potency Measures

A unit dose (1 mg/kg) would result in 100*exp(-Potency)% of background
activity

Potency: 6.892
se: 0.8802
var=se^2: 0.7748
Per cent. of background at unit dose: 0.1
Per cent. of background at the highest dose: 58
ED50 (95% CI): 0.1006 ( 0.0783 , 0.1292 )

ln(Potency) 1.93
se[log(Potency)]: 0.1277
se[log (Potency)]^2 : 0.01631
```

B-2. RBC and brain ChE activity in dams and fetuses from comparative ChE studies following gestational exposure

The following table (Table II.B.2 1) provides summary of RBC and brain ChE data from gestational exposure studies to dams and fetuses of selected OPs. The OPs included are the same as those selected for refined FQPA analysis (See I.B). DDVP is not included here as the laboratory reported unusually low control values which makes interpretation of the data problematic. EPA has asked that the dichlorovos comparative ChE study be repeated by the registrant.

For chemicals where only 'fetuses' are provided, the study reported data derived from samples where the male and female fetuses were pooled. The means and standard deviation are provided except for chlorpyrifos. The values provided in parentheses are calculated percent inhibition values. In the chlorpyrifos study, activity was reported as percent of control or as measured absorbance. For chlorpyrifos, the percent activity of control is listed.

Table II.B-2. 1 RBC and brain ChE activity in dams and fetuses from comparative ChE studies following gestational exposure.

OP	Cholinesterase & Group	Dose (mg/kg/day)				
	Dose	**0**	**0.5**	**1**	**2.5**	**10**
Acephate **MRID 46151805**	GD 21 Dams RBC Brain	1.6360 ± 0.7461 8.6009 ± 1.4779	1.9691 ± 0.7684 7.1673 ± 0.8621 (17)	2.3221 ± 0.5884 7.0441 ± 0.900 (18)	1.4638 ± 0.7615 5.096 ± 0.933 (41)	1.5202 ± 0.6202 3.3112 ± 0.5209 (62)
	GD 21 Fetuses RBC Brain	1.7284± 0.5776 1.4688 ± 0.0871	1.9883 ± 0.7651 1.3613 ± 0.1320	1.4476 ± 0.2403 1.2915 ± 0.1313 (12)	1.0662 ± 0.3121 1.2586 ± 0.1666 (14)	1.3385± 0.5334 0.8816 ± 0.1254 (40)
	Dose	**0**	**0.2**	**0.9**	**1.2**	
Azinphos methyl **MRID 46291101**	GD 20 Dams RBC Brain	1.43 ± 0.31 11.1 ± 0.5	1.41 ± 0.30 (1) 10.8 ± 0.7 (3)	1.39 ± 0.43 (3) 10.0 ± 1.9 (10)	1.05 ± 0.20 (27) 10.7± 0.7 (4)	
	GD 20 Fetuses RBC Brain	1.36 ± 0.28 2.2 ± 0.1	1.30 ± 0.07 (4) 2.3 ± 0.1	1.31 ± 0.15 (4) 2.3 ± 0.2	1.32 ± 0.17 (3) 2.2 ± 0.1 (0)	

OP	Cholinesterase & Group	Dose (mg/kg/day)			
Chlorpyrifos **MRID 44648102** **% activity compared to control**	**Dose**	**0**	**0.3**	**1**	**5**
	GD 20 Dams RBC Hindbrain		73.7**±14.5 101.1±7.2	17.6**±6.7 92.0*±2.2	4.9**±2.8 24.0**±4.8
	GD 20 Fetuses RBC Hindbrain		102.2±20.3 107.0±5.0	106.4±16.7 99.7±5.6	7.9**±4.3 46.1**±9.3
Diazinon **MRID 45842602**	**Dose**	**0**	**0.084**	**0.825**	**26.23**
	GD 20 Dams RBC Brain	1.106± 0.163 17.272± 1.041	1.183 ±0.165 16.925± 1.066	0.719± 0.223 (35) 16.675± 0.617	0.00± 0.00 (100) 3.228 ±0.229 (81.3)
	GD 20 Male fetuses RBC Brain	1.188± 0.230 2.383 ±0.194	1.392 ±0.183 2.380± 0.262	1.319± 0.230 2.194 ±0.161	0.247 ±0.162 (79.2) 1.689± 0.348 (29.1)
	GD 20 Female fetuses RBC Brain	1.208 ±0.143 2.311± 0.198	1.325± 0.172 2.360± 0.395	1.363± 0.254 2.231± 0.234	0.217± 0.148 (82.0) 1.822± 0.372 (21.2)
Dicrotophos **MRID 46153201**	**Dose**	**0**	**0.05**	**0.2**	**1.0**
	GD 20 Dams RBC Brain	2593 ± 218 4.78 ± 0.99	2342 ± 79 (10) 4.26± 1.06 (10)	1638± 120 (37) 2.49± 0.51 (48)	1282 ± 226 (51) 1.03 ± 0.21 (78)
	GD 20 Male fetuses RBC Brain	2546± 112 1.75± 0.34	2423± 351 1.51± 0.25 (14)	1923± 190 (24) 1.22± 0.28 (30)	1311± 124 (49) 0.77± 0.08 (56)

OP	Cholinesterase & Group	Dose (mg/kg/day)			
	GD 20 Female fetuses RBC Brain	 2523 ± 455 1.57± 0.18	 2362± 50 1.36± 0.13 (13)	 1825± 207 (28) 1.22± 0.11 (24)	 1414± 142 (44) 0.72± 0.02 (54)
Dimethoate **MRID 45529702**	**Dose**	**0.0**	**0.1**	**0.5**	**3.0**
	GD 20 Dams RBC Brain	 1669 ± 180 12,838 ± 1373	 1563 ± 224 (6) 13,044 ± 530 (-2)	 1459 ± 278 (13) 11,563 ± 300 (10)	 709 ± 104 (58) 5094 ± 1081 (60)
	GD 20 Fetuses RBC Brain	 1213 ± 79 1781 ± 175	 1225 ± 98 (-1) 1569 ± 173 (12)	 1181 ± 172 (3) 1600 ± 136 (10)	 834 ± 183 (31) 1188 ± 164 (33)
Disulfoton **MRID 46635901**	**Dose**	**0**	**0.042**	**0.168**	**0.694**
	GD 20 Dams RBC Brain	 2.02±0.34 11.97±0.53	 1.66±0.31 (18) 11.35±0.50 (5)	 1.13±0.37 (44) 8.12±0.44 (32)	 0.20±0.13 (90) 1.76±0.19 (85)
	GD 20 Fetuses RBC Brain	 1.27±0.16 1.81±0.30	 1.21±0.20 1.75±0.28	 1.02±0.19 (20) 1.74±0.26	 0.22±0.11 (83) 1.18±0.21 (35)
Fosthiazate **Not yet assigned**	**Dose**	**0**	**0.1**	**0.7**	**5**
	GD 20 Dams RBC Brain	 3931± 1474.5 49446± 2189.8	 3831 ± 757.3 48974 ± 1364.5	 2193 ± 712.2 (44) 47135 ± 1510 (5)	 20 ± 0.0 (99) 5152± 1718.9 (90)
	GD 20 Fetuses RBC Brain	 2644± 644.1 6612 ± 679.5	 3283 ± 992.4 6328 ± 476.3	 2893± 738.3 6251 ± 649.5 (5)	 1851 ± 593.4 (30) 5182 ± 684.5 (22)

OP	Cholinesterase & Group	Dose (mg/kg/day)			
	Dose	**0**	**0.10**	**1.03**	**3.12**
Methamidophos **MRID 46660901**	GD 20 Dams RBC Brain	 1.64 ± 0.286 10.82 ± 0.271	 1.68± 0.220 10.40± 1.711	 0.84± 0.117 (49) 4.86 ± 0.416 (55)	 0.45 ± 0.118 (73) 2.32± 0.173 (79)
	GD 20 Fetuses RBC Brain	 1.29 ± 0.196 1.56 ± 0.157	 1.13 ± 0.147 1.51± 0.089	 0.72 ± 0.133 (44) 1.08 ± 0.125 (31)	 0.38 ± 0.075 (55) 0.77 ± 0.061 (51)
	Dose	**0**	**0.03**	**0.30**	**0.60**
Methyl parathion **MRID 45646501**	GD 20 Dams RBC Brain	 1500.1 ± 255.03 13.48 ± 0.807	 1702.3 ± 386.36 13.58 ± 0.428	 979.5± 283.80 (35) 12.26 ± 0.527 (9)	 632.9± 124.52 (58) 9.35± 1.026 (31)
	GD 20 Male fetuses RBC Brain	 1041.3± 145.79 2.10± 0.116	 1082.2 ± 160.9 2.05± 0.095	 1075.0 ± 135.32 2.04 ± 0.173	 808.9 ± 186.38 (22) 1.97± 0.073
	GD 20 Female fetuses RBC Brain	 1090.4 ± 163.7 2.06 ± 0.152	 1118.0 ± 131.13 2.12 ± 0.14	 1010.2 ± 130.36 2.06 ± 0.174	 894.9± 215.77 (18) 2.02 ± 0.092
	Dose	**0**	**0.03**	**0.1**	**0.2**
Phorate **MRID 46241402**	GD 20 Dams RBC Brain	 35.98 ± 1.12 2.95 ± 0.54	 33.92 ± 3.76 2.88 ± 0.74	 30.99 ± 4.82 (14) 2.94± 0.70	 27.64 ± 5.16 (23) 1.73 ± 0.67 (41)
	GD 20 Male fetuses RBC Brain	 7.05 ± 0.83 0.57 ± 0.01	 5.72 ± 0.51 (19) 0.58 ± 0.04	 5.69 ± 0.66 (19) 0.56± 0.03	 6.42 ± 0.56 0.60 ± 0.03 (6)
	GD 20 Female fetuses RBC Brain	 6.80± 0.99 0.59± 0.04	 5.81± 0.91 0.57 ± 0.04	 5.48± 0.89 0.58± 0.02	 6.28 ± 0.78 0.59 ± 0.02

OP	Cholinesterase & Group	Dose (mg/kg/day)			
	Dose	**0**	**0.03**	**0.1**	**0.3/0.2**
Terbufos **MRID 46240802**	GD 20 Dams RBC Brain	 42.30 ± 5.00 3.00 ± 1.12	 40.68 ± 4.00 3.00± 0.79	 14.42± 4.04 (66) 1.96± 0.68 (35)	 4.46± 1.64 (89) 0.69± 0.19 (77)
	GD 20 Male fetuses RBC Brain	 5.16 ± 1.48 0.59± 0.11	 4.63 ± 1.86 0.53± 0.05	 2.51± 0.86 (51) 0.48± 0.04 (19)	 1.62 ± 0.69 (69) 0.36 ± 0.09 (39)
	GD 20 Female fetuses RBC Brain	 4.32 ± 0.85 0.53 ± 0.04	 4.52 ± 0.99 0.57 ± 0.04	 1.99± 1.09 (54) 0.50± 0.05	 1.76 ± 0.75 (59) 0.36± 0.07 (32)

B-3. Cholinesterase data used in OP CRA to derive RPFs and PoDs

See file: OPChEData_06-02-rev.xls

B-4. Spreadsheet with data from repeated dosing comparative ChE studies (juvenile and adult rats)

See file: Compcherepeated.xls

C-1. The Sources of Residue Inputs for the Assessment of the Cumulative Dietary Exposure to Organophosphorus Pesticides on Foods

See file II_C1.xls

Foods in CSFII 1994-1998 are listed in descending order of per capita consumption by children

C-2. Summary of PDP Residue Analyses of Organophosphorus Pesticides on Foods (1994-2004)

See file II_C_2.xls

C-3. A summary of FDA Total Diet Study Analyses for Organophosphorus Pesticides in Meats (1991-2001)

Table II.C-3.1 A summary of FDA Total Diet Study Analyses for Organophosphorus Pesticides in Meats (1991-2001).

Food No	Sample Description	Year	Market Basket	Residue Found	Concentration (ppm)
017	ham, baked	1991	3	no residue found	0
017	ham, baked	1992	1	no residue found	0
017	ham, baked	1992	2	parathion	0.02
017	ham, baked	1992	2	phosalone	0.06
017	ham, baked	1993	1	no residue found	0
017	ham, baked	1993	2	no residue found	0
017	ham, baked	1993	3	no residue found	0
017	ham, baked	1994	1	no residue found	0
017	ham, baked	1994	2	no residue found	0
017	ham, baked	1994	3	parathion	0.02
017	ham, baked	1994	4	no residue found	0
017	ham, baked	1995	1	no residue found	0
017	ham, baked	1995	2	no residue found	0
017	ham, baked	1995	3	no residue found	0
017	ham, baked	1996	1	no residue found	0
017	ham, baked	1996	2	no residue found	0
017	ham, baked	1996	3	diazinon	0.01
017	ham, baked	1996	3	fenamiphos	0.03
017	ham, baked	1996	3	parathion	0.02
017	ham, baked	1996	4	no residue found	0
017	ham, baked	1997	1	no residue found	0
017	ham, baked	1997	2	no residue found	0
017	ham, baked	1997	3	no residue found	0

Food No	Sample Description	Year	Market Basket	Residue Found	Concentration (ppm)
017	ham, baked	1997	4	no residue found	0
017	ham, baked	1998	1	no residue found	0
017	ham, baked	1998	2	no residue found	0
017	ham, baked	1998	3	no residue found	0
017	ham, baked	1998	4	parathion	0.02
017	ham, baked	1998	4	profenofos	0.02
017	ham, baked	1998	4	terbufos	0.02
017	ham, baked	1999	1	no residue found	0
017	ham, baked	1999	2	no residue found	0
017	ham, baked	1999	3	no residue found	0
017	ham, baked	2000	1	no residue found	0
017	ham, baked	2000	2	no residue found	0
017	ham, baked	2000	3	no residue found	0
017	ham, baked	2000	4	no residue found	0
017	ham, baked	2001	1	no residue found	0
017	ham, baked	2001	2	no residue found	0
017	ham, baked	2001	3	demeton-S sulfone	0.1
017	ham, baked	2001	3	fenamiphos sulfoxide	0.04
017	ham, baked	2001	3	parathion	0.02
017	ham, baked	2001	4	no residue found	0
018	pork chop, pan-cooked	1991	3	no residue found	0
018	pork chop, pan-cooked	1992	1	no residue found	0
018	pork chop, pan-cooked	1992	2	no residue found	0
018	pork chop, pan-cooked	1993	1	no residue found	0
018	pork chop, pan-cooked	1993	2	no residue found	0
018	pork chop, pan-cooked	1993	3	parathion	0.02
018	pork chop, pan-cooked	1994	1	chlorpyrifos	0.002
018	pork chop, pan-cooked	1994	1	diazinon	0.0008
018	pork chop, pan-cooked	1994	1	parathion	0.02
018	pork chop, pan-cooked	1994	2	no residue found	0

Food No	Sample Description	Year	Market Basket	Residue Found	Concentration (ppm)
018	pork chop, pan-cooked	1994	3	no residue found	0
018	pork chop, pan-cooked	1994	4	no residue found	0
018	pork chop, pan-cooked	1995	1	no residue found	0
018	pork chop, pan-cooked	1995	2	no residue found	0
018	pork chop, pan-cooked	1995	3	no residue found	0
018	pork chop, pan-cooked	1996	1	no residue found	0
018	pork chop, pan-cooked	1996	2	diazinon	0.01
018	pork chop, pan-cooked	1996	2	parathion	0.02
018	pork chop, pan-cooked	1996	3	no residue found	0
018	pork chop, pan-cooked	1996	4	no residue found	0
018	pork chop, pan-cooked	1997	1	no residue found	0
018	pork chop, pan-cooked	1997	2	no residue found	0
018	pork chop, pan-cooked	1997	3	no residue found	0
018	pork chop, pan-cooked	1997	4	no residue found	0
018	pork chop, pan-cooked	1998	1	diazinon	0.01
018	pork chop, pan-cooked	1998	1	parathion	0.02
018	pork chop, pan-cooked	1998	1	trichlorfon	0.02
018	pork chop, pan-cooked	1998	2	no residue found	0
018	pork chop, pan-cooked	1998	3	no residue found	0
018	pork chop, pan-cooked	1998	4	no residue found	0
018	pork chop, pan-cooked	1999	1	no residue found	0
018	pork chop, pan-cooked	1999	2	no residue found	0
018	pork chop, pan-cooked	1999	3	no residue found	0
018	pork chop, pan-cooked	2000	1	no residue found	0
018	pork chop, pan-cooked	2000	2	azinphos-methyl oxygen analog	0.04
018	pork chop, pan-cooked	2000	2	diazinon	0.02
018	pork chop, pan-cooked	2000	2	fenthion oxygen analog sulfoxide	0.02
018	pork chop, pan-cooked	2000	2	naled	0.02
018	pork chop, pan-cooked	2000	2	parathion	0.02
018	pork chop, pan-cooked	2000	3	no residue found	0

Food No	Sample Description	Year	Market Basket	Residue Found	Concentration (ppm)
018	pork chop, pan-cooked	2000	4	no residue found	0
018	pork chop, pan-cooked	2001	1	no residue found	0
018	pork chop, pan-cooked	2001	2	no residue found	0
018	pork chop, pan-cooked	2001	3	no residue found	0
018	pork chop, pan-cooked	2001	4	chlorethoxyfos	0.02
018	pork chop, pan-cooked	2001	4	diazinon	0.02
018	pork chop, pan-cooked	2001	4	parathion	0.02
019	pork sausage, pan-cooked	1991	3	no residue found	0
019	pork sausage, pan-cooked	1992	1	no residue found	0
019	pork sausage, pan-cooked	1992	2	no residue found	0
019	pork sausage, pan-cooked	1993	1	no residue found	0
019	pork sausage, pan-cooked	1993	2	no residue found	0
019	pork sausage, pan-cooked	1993	3	no residue found	0
019	pork sausage, pan-cooked	1994	1	no residue found	0
019	pork sausage, pan-cooked	1994	2	no residue found	0
019	pork sausage, pan-cooked	1994	3	no residue found	0
019	pork sausage, pan-cooked	1994	4	no residue found	0
019	pork sausage, pan-cooked	1995	1	no residue found	0
019	pork sausage, pan-cooked	1995	2	no residue found	0
019	pork sausage, pan-cooked	1995	3	no residue found	0
019	pork sausage, pan-cooked	1996	1	no residue found	0
019	pork sausage, pan-cooked	1996	2	no residue found	0
019	pork sausage, pan-cooked	1996	3	no residue found	0
019	pork sausage, pan-cooked	1996	4	no residue found	0
019	pork sausage, pan-cooked	1997	1	no residue found	0
019	pork sausage, pan-cooked	1997	2	diazinon	0.01
019	pork sausage, pan-cooked	1997	2	ethion	0.002
019	pork sausage, pan-cooked	1997	2	methamidophos	0.02
019	pork sausage, pan-cooked	1997	2	parathion	0.02
019	pork sausage, pan-cooked	1997	3	ethion	0.003

Food No	Sample Description	Year	Market Basket	Residue Found	Concentration (ppm)
019	pork sausage, pan-cooked	1997	3	phosalone	0.003
019	pork sausage, pan-cooked	1997	4	no residue found	0
019	pork sausage, pan-cooked	1998	1	no residue found	0
019	pork sausage, pan-cooked	1998	2	ethion	0.002
019	pork sausage, pan-cooked	1998	3	acephate	0.02
019	pork sausage, pan-cooked	1998	3	diazinon	0.01
019	pork sausage, pan-cooked	1998	3	parathion	0.02
019	pork sausage, pan-cooked	1998	3	phosalone	0.04
019	pork sausage, pan-cooked	1998	4	no residue found	0
019	pork sausage, pan-cooked	1999	1	ethion	0.002
019	pork sausage, pan-cooked	1999	2	no residue found	0
019	pork sausage, pan-cooked	1999	3	no residue found	0
019	pork sausage, pan-cooked	2000	1	no residue found	0
019	pork sausage, pan-cooked	2000	2	ethion	0.003
019	pork sausage, pan-cooked	2000	3	no residue found	0
019	pork sausage, pan-cooked	2000	4	no residue found	0
019	pork sausage, pan-cooked	2001	1	no residue found	0
019	pork sausage, pan-cooked	2001	2	diazinon	0.04
019	pork sausage, pan-cooked	2001	2	fenthion oxygen analog	0.04
019	pork sausage, pan-cooked	2001	2	fenthion sulfone	0.08
019	pork sausage, pan-cooked	2001	2	parathion	0.04
019	pork sausage, pan-cooked	2001	3	no residue found	0
019	pork sausage, pan-cooked	2001	4	no residue found	0
020	pork bacon, pan-cooked	1991	3	no residue found	0
020	pork bacon, pan-cooked	1992	1	no residue found	0
020	pork bacon, pan-cooked	1992	2	no residue found	0
020	pork bacon, pan-cooked	1993	1	parathion	0.02
020	pork bacon, pan-cooked	1993	2	parathion	0.02
020	pork bacon, pan-cooked	1993	3	no residue found	0
020	pork bacon, pan-cooked	1994	1	no residue found	0

Food No	Sample Description	Year	Market Basket	Residue Found	Concentration (ppm)
020	pork bacon, pan-cooked	1994	2	no residue found	0
020	pork bacon, pan-cooked	1994	3	no residue found	0
020	pork bacon, pan-cooked	1994	4	no residue found	0
020	pork bacon, pan-cooked	1995	1	no residue found	0
020	pork bacon, pan-cooked	1995	2	no residue found	0
020	pork bacon, pan-cooked	1995	3	no residue found	0
020	pork bacon, pan-cooked	1996	1	no residue found	0
020	pork bacon, pan-cooked	1996	2	no residue found	0
020	pork bacon, pan-cooked	1996	3	no residue found	0
020	pork bacon, pan-cooked	1996	4	no residue found	0
020	pork bacon, pan-cooked	1997	1	azinphos-ethyl	0.2
020	pork bacon, pan-cooked	1997	1	diazinon	0.01
020	pork bacon, pan-cooked	1997	1	parathion	0.02
020	pork bacon, pan-cooked	1997	2	no residue found	0
020	pork bacon, pan-cooked	1997	3	no residue found	0
020	pork bacon, pan-cooked	1997	4	diazinon	0.01
020	pork bacon, pan-cooked	1997	4	parathion	0.02
020	pork bacon, pan-cooked	1997	4	trichlorfon	0.02
020	pork bacon, pan-cooked	1998	1	no residue found	0
020	pork bacon, pan-cooked	1998	2	no residue found	0
020	pork bacon, pan-cooked	1998	3	no residue found	0
020	pork bacon, pan-cooked	1998	4	no residue found	0
020	pork bacon, pan-cooked	1999	1	no residue found	0
020	pork bacon, pan-cooked	1999	2	no residue found	0
020	pork bacon, pan-cooked	1999	3	no residue found	0
020	pork bacon, pan-cooked	2000	1	no residue found	0
020	pork bacon, pan-cooked	2000	2	no residue found	0
020	pork bacon, pan-cooked	2000	3	no residue found	0
020	pork bacon, pan-cooked	2000	4	chlorpyrifos oxygen analog	0.2
020	pork bacon, pan-cooked	2000	4	dimethoate	0.04

Food No	Sample Description	Year	Market Basket	Residue Found	Concentration (ppm)
020	pork bacon, pan-cooked	2000	4	malathion oxygen analog	0.2
020	pork bacon, pan-cooked	2000	4	parathion	0.04
020	pork bacon, pan-cooked	2001	1	no residue found	0
020	pork bacon, pan-cooked	2001	2	no residue found	0
020	pork bacon, pan-cooked	2001	3	no residue found	0
020	pork bacon, pan-cooked	2001	4	no residue found	0
021	pork roast, baked	1991	3	no residue found	0
021	pork roast, baked	1992	1	no residue found	0
021	pork roast, baked	1992	2	no residue found	0
021	pork roast, baked	1993	1	no residue found	0
021	pork roast, baked	1993	2	no residue found	0
021	pork roast, baked	1993	3	no residue found	0
021	pork roast, baked	1994	1	no residue found	0
021	pork roast, baked	1994	2	no residue found	0
021	pork roast, baked	1994	3	no residue found	0
021	pork roast, baked	1994	4	no residue found	0
021	pork roast, baked	1995	1	ethion oxygen analog	0.02
021	pork roast, baked	1995	1	parathion	0.02
021	pork roast, baked	1995	2	no residue found	0
021	pork roast, baked	1995	3	no residue found	0
021	pork roast, baked	1996	1	no residue found	0
021	pork roast, baked	1996	2	no residue found	0
021	pork roast, baked	1996	3	no residue found	0
021	pork roast, baked	1996	4	azinphos-methyl	0.2
021	pork roast, baked	1996	4	diazinon	0.01
021	pork roast, baked	1996	4	parathion	0.02
021	pork roast, baked	1997	1	no residue found	0
021	pork roast, baked	1997	2	no residue found	0
021	pork roast, baked	1997	3	no residue found	0
021	pork roast, baked	1997	4	no residue found	0

Food No	Sample Description	Year	Market Basket	Residue Found	Concentration (ppm)
021	pork roast, baked	1998	1	no residue found	0
021	pork roast, baked	1998	2	no residue found	0
021	pork roast, baked	1998	3	diazinon	0.02
021	pork roast, baked	1998	3	omethoate	0.04
021	pork roast, baked	1998	3	parathion	0.02
021	pork roast, baked	1998	3	tribufos	0.02
021	pork roast, baked	1998	4	no residue found	0
021	pork roast, baked	1999	1	no residue found	0
021	pork roast, baked	1999	2	no residue found	0
021	pork roast, baked	1999	3	no residue found	0
021	pork roast, baked	2000	1	no residue found	0
021	pork roast, baked	2000	2	no residue found	0
021	pork roast, baked	2000	3	diazinon	0.02
021	pork roast, baked	2000	3	fenthion oxygen analog sulfoxide	0.1
021	pork roast, baked	2000	3	naled	0.1
021	pork roast, baked	2000	3	parathion	0.02
021	pork roast, baked	2000	4	no residue found	0
021	pork roast, baked	2001	1	no residue found	0
021	pork roast, baked	2001	2	diazinon	0.02
021	pork roast, baked	2001	2	fenthion oxygen analog	0.02
021	pork roast, baked	2001	2	fenthion sulfone	0.04
021	pork roast, baked	2001	2	parathion	0.02
021	pork roast, baked	2001	3	no residue found	0
021	pork roast, baked	2001	4	no residue found	0
022	lamb chop, pan-cooked	1991	3	no residue found	0
022	lamb chop, pan-cooked	1992	1	no residue found	0
022	lamb chop, pan-cooked	1992	2	no residue found	0
022	lamb chop, pan-cooked	1993	1	no residue found	0
022	lamb chop, pan-cooked	1993	2	no residue found	0
022	lamb chop, pan-cooked	1993	3	no residue found	0

Food No	Sample Description	Year	Market Basket	Residue Found	Concentration (ppm)
022	lamb chop, pan-cooked	1994	1	chlorpyrifos	0.006
022	lamb chop, pan-cooked	1994	1	diazinon	0.009
022	lamb chop, pan-cooked	1994	1	parathion	0.02
022	lamb chop, pan-cooked	1994	2	no residue found	0
022	lamb chop, pan-cooked	1994	3	diazinon	0.002
022	lamb chop, pan-cooked	1994	4	parathion	0.02
022	lamb chop, pan-cooked	1995	1	no residue found	0
022	lamb chop, pan-cooked	1995	2	no residue found	0
022	lamb chop, pan-cooked	1995	3	no residue found	0
022	lamb chop, pan-cooked	1996	1	no residue found	0
022	lamb chop, pan-cooked	1996	2	no residue found	0
022	lamb chop, pan-cooked	1996	3	no residue found	0
022	lamb chop, pan-cooked	1996	4	no residue found	0
022	lamb chop, pan-cooked	1997	1	no residue found	0
022	lamb chop, pan-cooked	1997	2	no residue found	0
022	lamb chop, pan-cooked	1997	3	diazinon	0.01
022	lamb chop, pan-cooked	1997	3	mevinphos, (e)-	0.01
022	lamb chop, pan-cooked	1997	3	parathion	0.02
022	lamb chop, pan-cooked	1997	4	no residue found	0
022	lamb chop, pan-cooked	1998	1	no residue found	0
022	lamb chop, pan-cooked	1998	2	no residue found	0
022	lamb chop, pan-cooked	1998	3	no residue found	0
022	lamb chop, pan-cooked	1998	4	no residue found	0
022	lamb chop, pan-cooked	1999	1	chlorpyrifos	0.0002
022	lamb chop, pan-cooked	1999	2	diazinon	0.02
022	lamb chop, pan-cooked	1999	2	disulfoton sulfone	0.02
022	lamb chop, pan-cooked	1999	2	ethoprop	0.02
022	lamb chop, pan-cooked	1999	2	parathion	0.02
022	lamb chop, pan-cooked	1999	3	cadusafos	0.02
022	lamb chop, pan-cooked	1999	3	diazinon	0.002

Food No	Sample Description	Year	Market Basket	Residue Found	Concentration (ppm)
022	lamb chop, pan-cooked	1999	3	diazinon	0.02
022	lamb chop, pan-cooked	1999	3	parathion	0.02
022	lamb chop, pan-cooked	2000	1	no residue found	0
022	lamb chop, pan-cooked	2000	2	no residue found	0
022	lamb chop, pan-cooked	2000	3	no residue found	0
022	lamb chop, pan-cooked	2000	4	no residue found	0
022	lamb chop, pan-cooked	2001	1	no residue found	0
022	lamb chop, pan-cooked	2001	2	no residue found	0
022	lamb chop, pan-cooked	2001	3	no residue found	0
022	lamb chop, pan-cooked	2001	4	no residue found	0
029	bologna, sliced	1991	3	no residue found	0
029	bologna, sliced	1992	1	no residue found	0
029	bologna, sliced	1992	2	no residue found	0
029	bologna, sliced	1993	1	no residue found	0
029	bologna, sliced	1993	2	no residue found	0
029	bologna, sliced	1993	3	no residue found	0
029	bologna, sliced	1994	1	no residue found	0
029	bologna, sliced	1994	2	no residue found	0
029	bologna, sliced	1994	3	no residue found	0
029	bologna, sliced	1994	4	no residue found	0
029	bologna, sliced	1995	1	no residue found	0
029	bologna, sliced	1995	2	no residue found	0
029	bologna, sliced	1995	3	no residue found	0
029	bologna, sliced	1996	1	no residue found	0
029	bologna, sliced	1996	2	no residue found	0
029	bologna, sliced	1996	3	diazinon	0.01
029	bologna, sliced	1996	3	fenamiphos	0.03
029	bologna, sliced	1996	3	parathion	0.02
029	bologna, sliced	1996	4	no residue found	0
029	bologna, sliced	1997	1	no residue found	0

Food No	Sample Description	Year	Market Basket	Residue Found	Concentration (ppm)
029	bologna, sliced	1997	2	no residue found	0
029	bologna, sliced	1997	3	no residue found	0
029	bologna, sliced	1997	4	no residue found	0
029	bologna, sliced	1998	1	diazinon	0.01
029	bologna, sliced	1998	1	DDVP	0.02
029	bologna, sliced	1998	1	parathion	0.02
029	bologna, sliced	1998	2	no residue found	0
029	bologna, sliced	1998	3	no residue found	0
029	bologna, sliced	1998	4	no residue found	0
029	bologna, sliced	1999	1	no residue found	0
029	bologna, sliced	1999	2	no residue found	0
029	bologna, sliced	1999	3	no residue found	0
029	bologna, sliced	2000	1	no residue found	0
029	bologna, sliced	2000	2	azinphos-methyl oxygen analog	0.08
029	bologna, sliced	2000	2	diazinon	0.04
029	bologna, sliced	2000	2	fenthion oxygen analog sulfoxide	0.04
029	bologna, sliced	2000	2	naled	0.04
029	bologna, sliced	2000	2	parathion	0.04
029	bologna, sliced	2000	3	no residue found	0
029	bologna, sliced	2000	4	no residue found	0
029	bologna, sliced	2001	1	no residue found	0
029	bologna, sliced	2001	2	no residue found	0
029	bologna, sliced	2001	3	no residue found	0
029	bologna, sliced	2001	4	no residue found	0
030	salami, sliced	1991	3	no residue found	0
030	salami, sliced	1992	1	no residue found	0
030	salami, sliced	1992	2	no residue found	0
030	salami, sliced	1993	1	no residue found	0
030	salami, sliced	1993	2	no residue found	0
030	salami, sliced	1993	3	no residue found	0

Food No	Sample Description	Year	Market Basket	Residue Found	Concentration (ppm)
030	salami, sliced	1994	1	no residue found	0
030	salami, sliced	1994	2	no residue found	0
030	salami, sliced	1994	3	no residue found	0
030	salami, sliced	1994	4	no residue found	0
030	salami, sliced	1995	1	no residue found	0
030	salami, sliced	1995	2	no residue found	0
030	salami, sliced	1995	3	no residue found	0
030	salami, sliced	1996	1	no residue found	0
030	salami, sliced	1996	2	diazinon	0.01
030	salami, sliced	1996	2	parathion	0.02
030	salami, sliced	1996	3	no residue found	0
030	salami, sliced	1996	4	no residue found	0
030	salami, sliced	1997	1	no residue found	0
030	salami, sliced	1997	2	diazinon	0.01
030	salami, sliced	1997	2	methamidophos	0.02
030	salami, sliced	1997	2	parathion	0.02
030	salami, sliced	1997	3	no residue found	0
030	salami, sliced	1997	4	no residue found	0
030	salami, sliced	1998	1	no residue found	0
030	salami, sliced	1998	2	no residue found	0
030	salami, sliced	1998	3	no residue found	0
030	salami, sliced	1998	4	no residue found	0
030	salami, sliced	1999	1	no residue found	0
030	salami, sliced	1999	2	no residue found	0
030	salami, sliced	1999	3	no residue found	0
030	salami, sliced	2000	1	no residue found	0
030	salami, sliced	2000	2	azinphos-methyl oxygen analog	0.04
030	salami, sliced	2000	2	diazinon	0.02
030	salami, sliced	2000	2	fenthion oxygen analog sulfoxide	0.02
030	salami, sliced	2000	2	naled	0.02

Food No	Sample Description	Year	Market Basket	Residue Found	Concentration (ppm)
030	salami, sliced	2000	2	parathion	0.02
030	salami, sliced	2000	3	no residue found	0
030	salami, sliced	2000	4	chlorpyrifos oxygen analog	0.1
030	salami, sliced	2000	4	dimethoate	0.02
030	salami, sliced	2000	4	malathion oxygen analog	0.1
030	salami, sliced	2000	4	parathion	0.02
030	salami, sliced	2001	1	no residue found	0
030	salami, sliced	2001	2	no residue found	0
030	salami, sliced	2001	3	no residue found	0
030	salami, sliced	2001	4	no residue found	0
238	veal cutlet, pan-cooked	1991	3	no residue found	0
238	veal cutlet, pan-cooked	1992	1	no residue found	0
238	veal cutlet, pan-cooked	1992	2	no residue found	0
238	veal cutlet, pan-cooked	1993	1	parathion	0.02
238	veal cutlet, pan-cooked	1993	2	no residue found	0
238	veal cutlet, pan-cooked	1993	3	parathion	0.02
238	veal cutlet, pan-cooked	1994	1	parathion	0.02
238	veal cutlet, pan-cooked	1994	2	no residue found	0
238	veal cutlet, pan-cooked	1994	3	malathion	0.001
238	veal cutlet, pan-cooked	1994	4	no residue found	0
238	veal cutlet, pan-cooked	1995	1	no residue found	0
238	veal cutlet, pan-cooked	1995	2	no residue found	0
238	veal cutlet, pan-cooked	1995	3	no residue found	0
238	veal cutlet, pan-cooked	1996	1	no residue found	0
238	veal cutlet, pan-cooked	1996	2	no residue found	0
238	veal cutlet, pan-cooked	1996	3	no residue found	0
238	veal cutlet, pan-cooked	1996	4	azinphos-methyl	0.2
238	veal cutlet, pan-cooked	1996	4	diazinon	0.01
238	veal cutlet, pan-cooked	1996	4	parathion	0.02
238	veal cutlet, pan-cooked	1997	1	no residue found	0

Food No	Sample Description	Year	Market Basket	Residue Found	Concentration (ppm)
238	veal cutlet, pan-cooked	1997	2	no residue found	0
238	veal cutlet, pan-cooked	1997	3	no residue found	0
238	veal cutlet, pan-cooked	1997	4	no residue found	0
238	veal cutlet, pan-cooked	1998	1	no residue found	0
238	veal cutlet, pan-cooked	1998	2	no residue found	0
238	veal cutlet, pan-cooked	1998	3	no residue found	0
238	veal cutlet, pan-cooked	1998	4	parathion	0.02
238	veal cutlet, pan-cooked	1998	4	profenofos	0.02
238	veal cutlet, pan-cooked	1998	4	terbufos	0.02
238	veal cutlet, pan-cooked	1999	1	no residue found	0
238	veal cutlet, pan-cooked	1999	2	no residue found	0
238	veal cutlet, pan-cooked	1999	3	no residue found	0
238	veal cutlet, pan-cooked	2000	1	no residue found	0
238	veal cutlet, pan-cooked	2000	2	no residue found	0
238	veal cutlet, pan-cooked	2000	3	no residue found	0
238	veal cutlet, pan-cooked	2000	4	no residue found	0
238	veal cutlet, pan-cooked	2001	1	no residue found	0
238	veal cutlet, pan-cooked	2001	2	no residue found	0
238	veal cutlet, pan-cooked	2001	3	demeton-S sulfone	0.1
238	veal cutlet, pan-cooked	2001	3	fenamiphos sulfoxide	0.04
238	veal cutlet, pan-cooked	2001	3	parathion	0.02
238	veal cutlet, pan-cooked	2001	4	no residue found	0
239	ham luncheon meat, sliced	1991	3	no residue found	0
239	ham luncheon meat, sliced	1992	1	no residue found	0
239	ham luncheon meat, sliced	1992	2	parathion	0.02
239	ham luncheon meat, sliced	1992	2	phosalone	0.06
239	ham luncheon meat, sliced	1993	1	no residue found	0
239	ham luncheon meat, sliced	1993	2	no residue found	0
239	ham luncheon meat, sliced	1993	3	no residue found	0
239	ham luncheon meat, sliced	1994	1	no residue found	0

Food No	Sample Description	Year	Market Basket	Residue Found	Concentration (ppm)
239	ham luncheon meat, sliced	1994	2	no residue found	0
239	ham luncheon meat, sliced	1994	3	parathion	0.02
239	ham luncheon meat, sliced	1994	4	no residue found	0
239	ham luncheon meat, sliced	1995	1	ethion oxygen analog	0.02
239	ham luncheon meat, sliced	1995	1	parathion	0.02
239	ham luncheon meat, sliced	1995	2	diazinon	0.01
239	ham luncheon meat, sliced	1995	2	parathion	0.02
239	ham luncheon meat, sliced	1995	3	no residue found	0
239	ham luncheon meat, sliced	1996	1	no residue found	0
239	ham luncheon meat, sliced	1996	2	no residue found	0
239	ham luncheon meat, sliced	1996	3	no residue found	0
239	ham luncheon meat, sliced	1996	4	no residue found	0
239	ham luncheon meat, sliced	1997	1	no residue found	0
239	ham luncheon meat, sliced	1997	2	no residue found	0
239	ham luncheon meat, sliced	1997	3	no residue found	0
239	ham luncheon meat, sliced	1997	4	no residue found	0
239	ham luncheon meat, sliced	1998	1	diazinon	0.01
239	ham luncheon meat, sliced	1998	1	DDVP	0.02
239	ham luncheon meat, sliced	1998	1	parathion	0.02
239	ham luncheon meat, sliced	1998	2	no residue found	0
239	ham luncheon meat, sliced	1998	3	no residue found	0
239	ham luncheon meat, sliced	1998	4	no residue found	0
239	ham luncheon meat, sliced	1999	1	no residue found	0
239	ham luncheon meat, sliced	1999	2	no residue found	0
239	ham luncheon meat, sliced	1999	3	no residue found	0
239	ham luncheon meat, sliced	2000	1	no residue found	0
239	ham luncheon meat, sliced	2000	2	no residue found	0
239	ham luncheon meat, sliced	2000	3	no residue found	0
239	ham luncheon meat, sliced	2000	4	no residue found	0
239	ham luncheon meat, sliced	2001	1	no residue found	0

Food No	Sample Description	Year	Market Basket	Residue Found	Concentration (ppm)
239	ham luncheon meat, sliced	2001	2	diazinon	0.02
239	ham luncheon meat, sliced	2001	2	fenthion oxygen analog	0.02
239	ham luncheon meat, sliced	2001	2	fenthion sulfone	0.04
239	ham luncheon meat, sliced	2001	2	parathion	0.02
239	ham luncheon meat, sliced	2001	3	no residue found	0
239	ham luncheon meat, sliced	2001	4	no residue found	0

C-4. Permissible Crop Translations for Pesticide Monitoring Data Table

Table II.C-4.1 Permissible Crop Translations for Pesticide Monitoring Data[24].

Commodity Analyzed	Commodity translated to...	Comments
Potato	Subgroup 1-C	
Carrot	Subgroup 1-A or 1-C	
Head Lettuce	Cabbage, Chinese cabbage napa (tight headed varieties), Brussels sprouts, radicchio	All have a head morphology best represented by lettuce. All are in Subgroup 5A except radicchio (4-A).
Broccoli	Cauliflower, Chinese broccoli, Chinese cabbage bok choy, Chinese mustard, kohlrabi	Broccoli better represents these heading, thickly stemmed and/or more branching cole crops than spinach does.
Spinach	Subgroup 4-A, Subgroup 5-B and Subgroup 4-B (except celery and fennel unless a strong case can be made)	Celery and fennel typically are excluded since residues may be higher in these crops due to the whorled, overlapping petioles which may retain spray residues.
Green Bean	Subgroups 6-A and 6-B	
Soybean	Subgroup 6-C	
Tomato or bell pepper	Group 8	All are fruiting vegetables.
Cucumber	Subgroup 9-B	All are cucurbit vegetables; residues in melon and pumpkin expected to be lower because of removal of rind.
Cantaloupe or Winter squash	Subgroup 9-A and pumpkin	
Orange	Group 10	Fruit will be peeled before analysis by PDP.
Apple or Pear	Group 11	All are pome fruits.
Peach	Group 12, except cherries (sweet and tart)	All are stone fruits.
Grape	Kiwifruit	Based on similar cultural practices.
Wheat	Group 15, except corn, rice, or wild rice	All are small grain crops or closely related thereto.
Milk	Meat	Metabolism study must indicate that residues in meat, fat, and meat-by-products will likely be equal to or lower than residues in milk. If dermal use is allowed on beef cattle, then it must be permitted and used on dairy cattle as well.

[24] Extracted from OPP/HED SOP 99.3

C-5. Processing Factors Used in Estimating Residues of OP Pesticides in Food Commodities

See file II_C_5.xls

C-6. Translation of Residue Source Data to CSFII Food Forms

See file II_C_6.xls

C-7. Summary of Residue Distribution Inputs to DEEM-FCID for Cumulative OP Exposure Assessment

See file II_C_7.xls

C-8. Analysis of Chemicals and Foods in the Upper Portion of OP Cumulative Exposure Distribution for Children 3-5 Years Old

See file II_C_8.xls

C-9. Co-Occurrence of Organophosphorus Pesticides on PDP Samples, 1994-2004

See file II.C_9.xls

D-1. Supplemental Distributions of Exposure Data Incorporated in the Residential Assessment

Study Summary

MRID 410547-05 (Exposures of Applicators to Propoxur during Residential Application of an Aerosol Spray Containing 1% Propoxur): Applicators in the study each applied one 16-ounce aerosol can in each of the 15 residences situated in Vero Beach, Florida. The entire contents were applied to each house. The volunteers sprayed to cracks, crevices along baseboards and other woodwork, under sinks and behind appliances. The majority of the exposure was to the hands, neck and head (~85%).

Unit Exposure Data

Table II.D-1.1 Dermal Unit Exposure Data (MRID 41054705) Used for Indoor Aerosol Applicator Scenarios)

Dermal Unit Exposure Values (mg/oz ai handled)
5.4
5.3
7
3.4
2.3
3
7.1
2.5
3.4
0.9
3.8
0.98
2.7
0.85
0.85

Table II.D-1.2 Inhalation Unit Exposure Data (MRID 41054705 Used for Indoor Aerosol Applicator Scenarios)

Inhalation Unit Exposure Values (mg/oz ai handled)
0.33
0.043
0.51
0.38
0.49
0.48
0.42
0.35
0.56
0.16
0.25
0.22
0.25
0.1
0.14

Statistical Analysis Details

Distributional parameters were estimated for the dermal unit exposure (Table II.D.1 1) and inhalation unit exposure (Table II.D.1 2) values for pressurized can sprayer applications of propoxur. Both unit exposure values are expressed in terms of milligrams per ounce of active ingredient applied. The dermal and inhalation unit exposure values were assumed to be lognormally distributed (i.e. fitted with a lognormal distribution). For these datasets, the shape (α) and scale (β) lognormal parameters were estimated by calculating the mean and standard deviation of the natural logarithms (base e) of the dermal and inhalation unit exposure values, respectively. Parametric estimates of the arithmetic mean (μ) and standard deviation (σ) of the lognormal distribution were then calculated based on the shape and scale parameter estimates. The formulae used to calculate the mean and standard deviation are given below

$$\mu = \exp(\alpha + \tfrac{1}{2}\beta^2)$$

$$\sigma = \mu\sqrt{\exp(\beta^2) - 1}$$

Shapiro-Wilk (S-W) normality test statistics were used to assess the lognormal assumption implicit in the parametric calculations of the mean and standard deviation. The means, standard deviations, and p-values of

the S-W statistics are provided in Table II.D.1 3. A small p-value indicates that logarithms of the dermal and inhalation unit exposure values are not normally distributed, or equivalently, that the dermal and inhalation unit exposure values are not lognormally distributed. For both the dermal and inhalation pressurized can datasets, the S-W p-values are greater than 0.05.

Table II.D-1.3 Lognormal Distributions of Dermal and Inhalation Unit Exposure Values Used for Indoor Aerosol Applicator Scenarios)

Application Method	Exposure Route	Deposition (mg/cm^2) and Air Concentration (mg/m^3) Distributions	Shapiro-Wilk p-value
Handheld Aerosol Spray Can	Dermal	LN(10.03, 12.84)	0.069
	Inhalation	LN(0.34, 0.27)	0.063
NOTES: LN(μ, σ) represents a lognormal distribution with mean=μ and standard deviation=σ.			

Additionally, probability plots were used to qualitatively assess the appropriateness of the lognormal assumptions. Generally a probability plot displays the actual values of a dataset (represented as points) and their expected values (represented as a line) for the specified distribution. The closer the actual values are to their expected values (i.e. the more the actual values approximate a straight line), the more likely the dataset is of the specified distribution. The probability plots for the dermal and inhalation unit exposure datasets are provided in Figures II.D.1 1 and 2. The probability plots indicate that both datasets are reasonably approximated by lognormal distributions.

Figure II.D-1.1 Dermal Unit Exposure Probability Plot

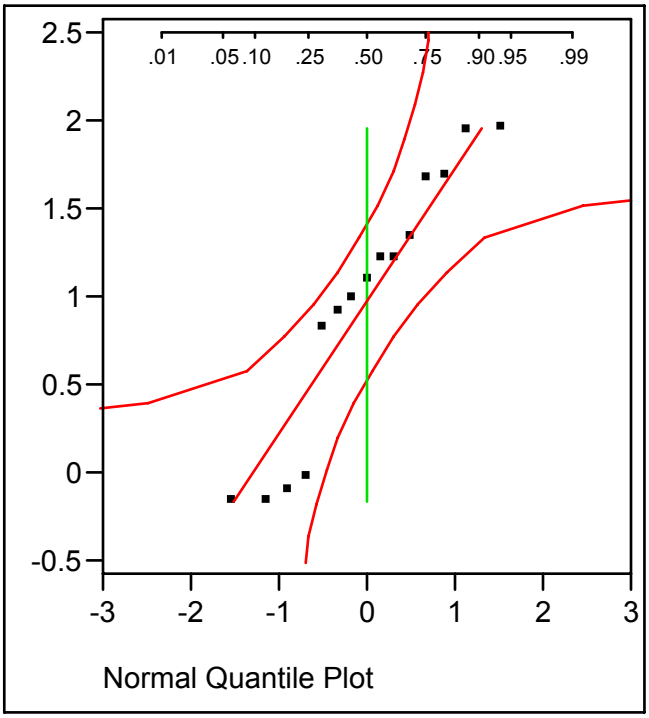
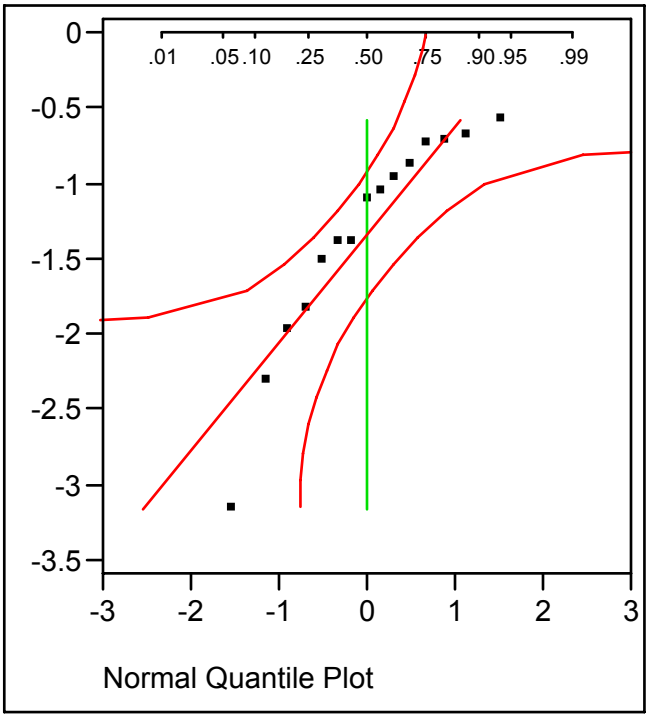


Figure II.D-1.2 Inhalation Unit Exposure Probability Plot



E-1. OP Cumulative Exposure in Drinking Water: The Effects of Water Chlorination on Organophosphate (OP) Pesticides (Phase I)

This report is an addendum to the 2002 OP CRA drinking water appendix II.E.4 – Effects of Drinking Water Treatment on Organophosphate Pesticides. Phase I of this study evaluated the potential of ten OP pesticides to form oxons as a result oxidation during drinking water treatment processes. Phase II of the study evaluated the potential of the sulfone and sulfoxide transformation products of disulfoton, phorate, and terbufos to form oxons.

The studies were conducted by the USEPA Office of Pesticide Program (OPP) Biological and Economic Analysis Division (BEAD) laboratories and have been reviewed by the USEPA Office of Research and Development (ORD). The results support the oxon characterization in the drinking water exposure assessment for the 2006 OP CRA.

1. Executive Summary – Phase I

Ten organophosphate (OP) pesticides [phorate, disulfoton, terbufos, methidathion, bensulide, chlorethoxyfos, phosmet, methyl parathion, phostebupirim, and temephos] were evaluated for their potential to undergo oxidation to their respective oxons in laboratory water simulating the chlorination process in drinking water facilities over a 72 hour exposure period. Samples were collected after 0, 1, 4, 24, and 72 hours of chlorination and analyzed by both gas chromatography-mass selective detection (GC-MSD) and liquid chromatography-tandem mass spectrometry (LC/MS/MS) to determine the presence of the pesticides and their oxons.

The results show that only two of the ten OP pesticides [methidathion and methyl parathion] are stable in buffered water (without chlorination) over the 72 hour exposure period. The eight remaining OP pesticides [phorate, disulfoton, terbufos, bensulide, chlorethyoxyfos, phostebupirim, phosmet, and temephos] were unstable and degraded in the buffered water over the 72 hour exposure period.

The results also show that in chlorinated water, three of the ten OP pesticides [phorate, disulfoton, and terbufos] did not undergo oxidation to their oxons under the experiment conditions. Phosmet oxon was initially formed; however, it degraded and was not detected after 24 hours. Five of the remaining six OP pesticides [methidathion, bensulide, chlorethyoxyfos, methyl parathion, and phostebupirim] formed stable oxons over the 72 exposure period. The oxon of the last remaining OP pesticide, temephos, is not commercially available and its presence could not be confirmed under

the experimental conditions. However, a full scan spectrum of the oxidation products from an exploratory LC/MS study revealed the presence of a compound with the same molecular ion profile as would be expected for the temephos oxon. Table II.E-1.1 summarizes the results of the experiment.

Table II.E-1.1 Results for parameters examined in study.

OP Pesticide	Stability in water over 72 hours (no chlorination)	Oxon formation after 1 hour (upon chlorination)	Oxon stability after 72 hours
Phorate	Poor	No	-
Disulfoton	Poor	No	-
Terbufos	Poor	No	-
Methidathion	Good	Yes	Good
Bensulide	Poor	Yes	Good
Chlorethoxyfos	Poor	Yes	Good
Methyl parathion	Good	Yes	Good
Phosmet	Poor	Yes	Poor
Phostebupirim	Poor	Yes	Good
Temephos	Poor	Possible (not confirmed)	n/a

In accordance with the Quality Assurance Project Plan (QAPP) for study, there were two elements necessary for the strict qualitative interpretation whether the ten OP pesticides underwent oxidative desulfonation during a 72 hour contact time in chlorinated laboratory water. This conclusion would be reached if the oxons are detected at any quantifiable level in either replication in the chlorinated laboratory water treatments at any sampling time and the OP pesticides are stable in non-chlorinated laboratory water. Only methidathion and methyl parathion met those criteria.

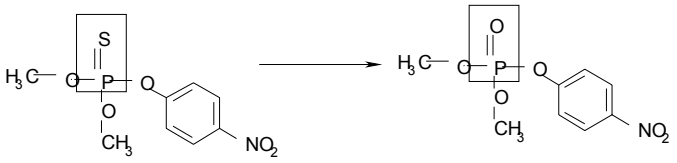
2. Introduction

The application of pesticides in arable lands has resulted in the contamination of natural waters such as surface water and groundwater. The initial contamination at the application sites has spread via surface runoff to nearby lakes, rivers, and streams and through subsurface transport to aquifers. The contaminated surface waters and ground waters are eventually used as source or raw waters in some community drinking water systems. After subjecting the raw water to different treatment processes in the water purification facilities, the concentrations of the pesticides may change or remain essentially the same in the treated or final drinking water. Studies conducted by scientists at EPA's ORD in Cincinnati (Miltner et al, 1989) indicate that conventional treatment (coagulation/clarification, filtration, softening, recarbonation, and chlorination) are generally not effective in removing certain pesticides from

raw water. However, other pesticides are unstable in the presence of chemical disinfectant such as chlorine.

Previous studies in Japan (Magara et al, 1994) and United States (Tierney et al, 2001; Duirk and Collette, 2006) indicate that certain organophosphate pesticides can be transformed to their oxons during chemical disinfection by chlorine compounds. This chemical transformation process is shown in Figure III.E-1.1.

Figure II.E-1.1 Oxidative Desulfonation Reaction of an Organophosphate Pesticide in Chlorinated Water.



This transformation is a concern because chlorination is the most commonly used disinfection technique in many US drinking water treatment plants and the product oxons are generally considered to be more toxic than the parent compounds.

The Food Quality Protection Act of 1996 (FQPA) requires that all chemical pesticide residues in or on food be examined for any possible adverse health effects through exposure. Drinking water is one of the pathways for dietary exposure. Three organophosphate pesticides (diazinon, chlorpyrifos, and malathion) have been examined and have been found to transform during chlorination into their associated oxons. However, a number of other organophosphate pesticides have little or no data on their potential for transformation during these conditions. Consequently, data and additional information are needed on the probable oxidation of these organophosphate pesticides and the relative stability of oxons in chlorinated water. The ten organophosphate pesticides and their degradation products considered in this study are listed in Table II.E-1. 2.

Table II.E-1.2 Selected Organophosphate Pesticides from the Cumulative OP Assessment without Water Treatment Data on Chlorination Effects on Oxon Formation

OP Parent	OP Degradation Products
Phorate	phorate oxon phorate sulfoxide phorate sulfone phorate sulfoxide oxon phorate sulfone oxon
Disulfoton	disulfoton oxon disulfoton sulfoxide disulfoton sulfone disulfoton sulfoxide oxon disulfoton sulfone oxon
Terbufos	terbufos oxon terbufos sulfoxide terbufos sulfone terbufos sulfoxide oxon terbufos sulfone oxon
Methidathion	methidathion oxon
Bensulide	bensulide oxon
Chlorethoxyfos	chlorethoxyfos oxon
Methyl parathion	methyl paraoxon
Phosmet	phosmet oxon
Phostebupirim	phostebupirim oxon
Temephos	Temephos oxon (not available)

The objective of this study was to provide a qualitative screening level assessment on the potential for oxon formation in chlorinated laboratory water and the stability of the selected organophosphate pesticides in both un-chlorinated and chlorinated water and the stability of their respective oxons in the chlorinated laboratory water. There are approximately twenty organophosphate pesticides considered in the cumulative OP risk assessment. The ten selected pesticides being tested in this study consisted of the pesticides, which are capable of forming oxons, have outdoor use patterns, and have no chlorination water treatment data available. These data will be used in the revised cumulative OP risk assessment to characterize the potential for human exposure to oxons in treated water.

3. Project Description

The project description is listed in the study protocol in Appendix 1 (Section 7). A brief summary description follows:

For each of the ten OP pesticides to be tested, the experimental design consisted of:

- One replicate OP control [test water + OP pesticide, without chlorine]
- One replicate chlorine control [test water + chlorine]
- Two replicates of treatment [OP pesticide + test water + chlorine]
- One buffered water sample spiked with the ten pesticides and nine oxons at a concentration of ½ of the spiking concentration (50 ppb) at each sampling time.

Chlorination experiments were conducted in Fisher Environmental Grade reagent water to eliminate chlorine demand considerations. Similar testing conditions using laboratory waters are recommended as screening level testing for CCL water treatment studies and pesticide treatment studies at ORD. The chlorine dose in the laboratory water was equivalent to the recommended maximum disinfectant residual (RMDL) of 4 mg/L free chlorine concentration ± 10%. The pH of the Fisher reagent water was adjusted to pH 8 to represent typical water treatment conditions. The experiment was conducted for 72 hours with sampling times immediately prior to chlorination (~2 minutes after pesticide dosing), 1 hour, 4 hours, 24 hours, and 72 hours post chlorination. The 24 and 72 hour sampling times were selected to represent the treatment system water residence and/or distribution transport times of approximately 24 hr or longer. The pesticide concentration in the experiment was 100 ppb or below the solubility limit of the pesticide whichever is lower. The experiments were conducted using a mixture of the OP pesticides delivered to the system with low co-solvent concentrations or in the absence of co-solvents. The chlorine demand from co-solvents and degradation processes was determined by measuring free chlorine at each sampling interval.

4. Method and Materials

Fisher Scientific Certified Environmental Grade water was used as the test water. Water quality parameters of the test water were:

Test	Value	Unit
Color	< 5	APHA
Residue after Evaporation	< 1	ppm
Fluorescence (as quinine)	< 100	ppt
Resistivity	> 18	MΩ
Total Organic Carbon	< 20	ppb

Water samples were labeled clearly, and included date, time, and name of the preparer(s). To preserve the integrity of the data, all samples were stored at ~ 4^{o}C until extraction to minimize the physicochemical changes in the samples. If sample extraction into a solvent was necessary, extracts were stored below 0^{o}C and also analyzed as soon as possible. All samples used and generated during the study were properly disposed of.

Quality assurance samples consisted of:
1) reagent water blank – analysis of reagent water (one time only);
2) method blank – analysis of buffered reagent water plus chlorine; (time 1 hr);
3) non-chlorinated degradation check – analysis of buffered reagent water plus OPs; (time 0, 1, 4, 24, and 72 hrs);
4) matrix water blank – analysis of buffered reagent water (time 0);
5) matrix water spike – analysis of buffered reagent water plus 50 ppb of the OP parent(s) plus 50 ppb oxon(s) (one spike per analytical sample set).

These measures were classified as critical measurements and were prepared and analyzed with each group of samples to monitor laboratory contamination and method performance. Addition of surrogate compounds to environmental samples was also recommended to measure the efficiency of the method. The surrogate compounds was not normally found in the environment and was selected such that the interference with elution of target analytes and the effect from sample matrix were minimal.

a. Analytical Procedures

The analytical procedures used were able to accurately identify and measure the presence of the target analytes in the samples. Identification and quantitation of residues were by gas

chromatography-mass selective detection (GC/MSD) and/or liquid chromatography/tandem mass spectrometry (LC/MS/MS) techniques.

A calibration curve was constructed with mixtures(s) of pure standards (target analytes) with the spiking level and method detection limit as the bounding concentrations. Complete initial calibration curves were prepared monthly, and the individual calibration standards verified each day of operation.

In some cases, the analytical procedures were not completely developed to allow for complete quantification of the parent OP and its degradation products. Nevertheless, the analytical method was capable of providing clear separation of known pesticide residues on chromatograms to allow for residue identification.

b. Test Protocol

These studies were conducted at the OPP/BEAD/ACB Fort Meade and OPP/BEAD/ECB Stennis Space Center laboratories. A complete description of testing protocol can be found in the Appendix 1 (Section 7).

The control treatments were used to assess whether the OP pesticide undergoes oxidation in non-chlorinated laboratory water and to assess whether OP pesticide or its degradation products were in the chlorinated water without pesticide dosing. Because the experimental design had minimal replication and the analytical methods were not fully vetted for all the OP pesticides and their oxon degradation products, there was **strict qualitative interpretation** (i.e. presence or absence of oxon) on whether OP pesticides underwent oxidative desulfonation during a 72 hour contact time in chlorinated laboratory water. This deduction was reached if oxons were detected at any quantifiable level in either replication in the chlorinated laboratory water treatments at any sampling time and the OP pesticide was stable in non-chlorinated laboratory water. Additionally, the detection of oxons in chlorinated water at the 24 hour or 72 hour sampling times will suggest the oxon was stable enough in chlorinated water to have the potential for dietary exposure through drinking water

The primary focuses of these studies were the OP parent pesticides and their associated oxons, degradation products. Later studies will address the measurements of the sulfone, sulfoxide, sulfone oxon, and sulfoxide oxon degradation products for selected OP pesticides. Method detection and reporting limits will be reported in revisions to this QAPP once the analytical methods have been assessed.

c. Assessment and Oversight

A QA/QC laboratory audit was performed at the conclusion of the water chlorination studies with OP pesticides and their oxon degradation products. Subsequently, QA/QC audits will be performed at the conclusion of the water chlorination studies with certain OP pesticides and their sulfone, sulfoxide, sulfone oxon, and sulfoxide oxon.

5. Results

a. The Formation of Oxons from Ten OP Pesticides in Water

Ten organophosphate (OP) pesticides [phorate, disulfoton, terbufos, methidathion, bensulide, chlorethoxyfos, phosmet, methyl parathion, phostebupirim, and temephos] were evaluated for their potential to undergo oxidation to their respective oxons in laboratory water simulating the chlorination process in drinking water facilities. In these studies, the OP pesticides were dissolved into pH 8.0 buffered water and then chlorinated with a sodium hypochlorite solution. Over a 72 hour exposure period, water samples were collected, extracted whenever applicable, and analyzed by both gas chromatography-mass selective detection (GC-MSD) and liquid chromatography-tandem mass spectrometry (LC/MS/MS) to determine the presence of the pesticides and their oxons. The results are presented in Appendix 2 (Section 8) for both the GS-MSD and LC/MS/MS studies.

The results of both studies (GC-MSD & LC/MS/MS) showed that three of the ten OP pesticides (phorate, disulfoton, and terbufos) did not undergo oxidation into their oxons under the experiment conditions. Phosmet oxon was initially formed; however, it degraded and was not detected after 24 hours. Five of the remaining six OP pesticides [methidathion, bensulide, chlorethyoxyfos, methyl parathion, and phosetebuprim] formed stable oxons over the 72 exposure period. The oxon of the last remaining OP pesticide, temephos, is not commercially available and its presence could not be confirmed under the experimental conditions. However, a full scan spectrum of the oxidation products in an exploratory LC/MS study revealed the presence of a compound with the same molecular ion profile as would be expected for the temephos oxon. This exploratory study was conducted at a concentration of 5 ppm of temephos in chlorinated laboratory water. The detected compound increased in concentration during a 24 hour exposure period, simultaneously, with the decrease of the parent OP temephos. The lack of an authentic standard of the temephos oxon limits the complete confirmation of this oxon.

The analytical methods of GC-MSD and LC/MS/MS were complimentary to each other in the detection of all 10 OP pesticide parents and their oxons. The current GC/MSD conditions were not suitable for the detection of bensulide, while the LC/MS/MS conditions were not suitable for the detection of methyl parathion and chlorethoxyfos. However, their oxons were detectable under both method conditions.

b. The Stability of Ten OP Pesticides in Water

Ten organophosphate (OP) pesticides [phorate, disulfoton, terbufos, methidathion, bensulide, chlorethyoxyfos, phosmet, methyl parathion, phosetebuprim, and temephos] were evaluated in buffered laboratory water to act as a control to the separate studies of the pesticides in the buffered water during the chlorination process. In these studies the OP pesticides were dissolved into a pH 8.0 buffered water. Over a 72 hour exposure period, water samples were collected, extracted, and analyzed by both gas chromatography-mass selective detection (GC-MSD) and liquid chromatography-tandem mass spectrometry (LC/MS/MS) to determine the presence of the pesticides and their oxons without chlorination. The results are presented in Appendix 2 (Section 8) for both the GS-MSD and LC/MS/MS studies.

The results demonstrated that two of the ten OP pesticides [methidathion and methyl parathion], are stable in the buffered water without chlorination over the 72 hour exposure period. The eight remaining OP pesticides [phorate, disulfoton, terbufos, bensulide, chlorethyoxyfos, phosetebuprim, phosmet, and temephos] were unstable and degraded in the buffered water over the 72 hour exposure period.

c. The Stability of Free Chlorine Concentrations in Water

The concentration of chlorine as free chlorine was evaluated in buffered laboratory water to act as a control to the separate studies of the pesticides in the buffered water during the chlorination process. In these studies chlorine as free chlorine was added to a pH 8.0 buffered water. Over a 72 hour exposure period, water samples were collected and analyzed to determine the stable concentration of this form of chlorine. In both studies the concentration of free chlorine remained stable within 10% of the initial concentration and neither the OP pesticides nor their oxons were detected at any time during the 72 hour exposure period.

d. The Stability of 10 OP Pesticides and Their Oxons as Laboratory Control Spike Samples

Ten organophosphate (OP) pesticides [phorate, disulfoton, terbufos, methidathion, bensulide, chlorethyoxyfos, phosmet, methyl parathion, phosetebuprim, and temephos] and their nine available oxons [temephos oxon is not available] were spiked into pH 8.0 buffered laboratory water to act as laboratory control spike samples. These samples were used to assess the detection of these compounds at the time of analysis. The water samples were collected, spiked, extracted whenever applicable, and analyzed by both gas chromatography-mass selective detection (GC-MSD) and liquid chromatography-tandem mass spectrometry (LC/MS/MS) to determine the concentration of the pesticides and their oxons. The results are presented in Appendix 2 (Section 8) for both the GS-MSD and LC/MS/MS studies.

The results demonstrated that these pesticides, with the exception of methyl parathion and methidathion, were unstable and degrade in the buffered water if they were allowed to remain for any prolonged period prior to extraction and/or analysis. In the LC/MS/MS studies the laboratory control spike samples remained in the buffered water until analyzed. That time period could be as much as 4 hours. This resulted in varying degrees of degradation of the pesticides. In the GC-MSD studies the laboratory control spike samples were extracted at different time periods. For the D = 0 sample period the water sample was extracted within 1 hour, D = 4 sample period within 24 hours, and D = 72 within 1 minute. The results demonstrated that the longer the time between collections and extraction the less stable were the pesticides in water.

On the other hand, all nine oxons were stable in the buffered water prior to analysis in both of the studies.

6. Summary

There were two elements necessary to the strict qualitative interpretation whether these ten OP pesticides underwent oxidative desulfonation during a 72 hour contact time in chlorinated laboratory water. This conclusion could be reached if:

1) The oxons are detected at any quantifiable level in either replication in the chlorinated laboratory water treatments at any sampling time
   - o There were six quantifiable oxons detected in the chlorinated laboratory water within the seventy two hour exposure period

[methidathion oxon, methyl paraoxon, phosmet oxon, bensulide oxon, phostebupirim oxon, and chlorethoxyfos oxon].
- o There was mass spectral evidence of the possible formation of a seventh oxon [temephos oxon]. However, there is, at present, no authentic temephos oxon standard to positively confirm this result.

and

2) The OP pesticides are stable in non-chlorinated laboratory water.
   - o There were only two OP pesticides that were stable in the unchlorinated laboratory water [methidathion and methyl parathion].

3) Additionally, the detection of oxons in chlorinated water at the 24 hour or 72 hour sampling times would suggest the oxon is stable enough in chlorinated water to have the potential for dietary exposure through drinking water.
   - o Both of these oxons [methidathion oxon and methyl paraoxon] were stable at both the 24 hour and 72 hour sampling times.

Only methidathion and methyl parathion meet the criteria as established in the QAPP to conclude that they underwent oxidative desulfonation.

7. References

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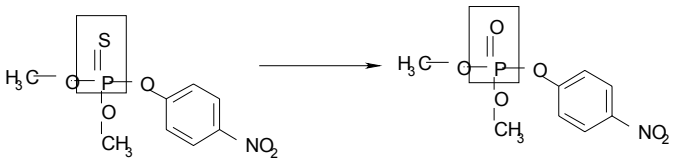
8. Appendix 1: Procedures for the Preliminary Laboratory Study on the Effects of Chlorinated Water on OP Pesticides

This appendix was prepared by the Water Treatment Effects Workgroup, Environmental Fate and Effects Division of the USEPA Office of Pesticide Programs on April 24, 2006.

a. Introduction

Previous studies in Japan (Magara et al, 1994) and United States (Tierney et al, 2001) indicate that certain organophosphate pesticides can be transformed during disinfection by chlorine compounds to oxons. This chemical transformation process is shown in Figure II.E-1.2.

Figure II.E-1.2 Oxidative Desulfonation Reaction of an Organophosphate Pesticide in Chlorinated Water.



This transformation is a concern because chlorination is widely used in many drinking water treatment plants and the product oxons are generally considered to be more toxic than the parent compounds. Consequently, data and additional information are needed on the probable oxidation of selected organophosphate pesticides and the relative stability of oxons in chlorinated water. The organophosphate pesticides and their degradation products considered in this testing protocol are listed in Table II.E-1.3.

Table II.E-1.1 Selected Organophosphate Pesticides from the Cumulative OP Assessment without Water Treatment Data on Chlorination Effects on Oxon Formation

OP Parent	OP Degradation Products
Phorate	phorate oxon phorate sulfoxide phorate sulfone phorate sulfoxide oxon phorate sulfone oxon
Disulfoton	disulfoton oxon disulfoton sulfoxide disulfoton sulfone disulfoton sulfoxide oxon disulfoton sulfone oxon
Terbufos	terbufos oxon terbufos sulfoxide terbufos sulfone terbufos sulfoxide oxon terbufos sulfone oxon
Methidathion	methidathion oxon
Bensulide	bensulide oxon
Chlorethoxyfos	chlorethoxyfos oxon
Methyl parathion	methyl paraoxon
Phosmet	phosmet oxon
Phostebupirim	phostebupirim oxon
Temephos	temephos oxon (not available)

Chlorination experiments will be conducted in Fisher certified environmental grade test water. Although the experiments will be conducted in environmental grade water, water pH (pH=8) will be altered to represent water treatment plant conditions. The chlorine dose in the laboratory water will be equivalent to the recommended maximum disinfectant residual (RMDL) of 4 mg/L free chlorine. Because the laboratory water will have extremely low chlorine demand, the free chlorine concentration and total chlorine concentration should be similar. The pH of the laboratory water will be adjusted to pH 8 to represent typical water treatment conditions. The experiment will be conducted for 72 hours with sampling times immediately prior to chlorination and 1 hour, 4 hours, 24 hours, and 72 hours post chlorination. The 24 and 72 hour sampling times were selected to represent the treatment system water residence and/or distribution transport times of approximately 24 hr or longer. The pesticide concentration in the experiment will be 100 ug/L or below the solubility limit of the pesticide whichever is lower. The experiments will be conducted using a mixture of the OP pesticides. The experiments will be conducted with low co-solvent concentrations or in the absence of co-solvents. The chlorine demand from co-solvents and

degradation processes will be determined by measuring free chlorine at each sampling interval.

The experimental plan will consist of a series of preliminary studies and final studies. These studies will be conducted by EPA personnel at the Biological and Economic Analysis Division Fort Meade Analytical Laboratory and Stennis Space Center Environmental Chemistry Laboratory. The chlorination study protocol and QAPP will be reviewed by Richard Miltner, P.E. from the ORD/NRMRL/Water Supply and Water Resources Division/ Treatment Technology Evaluation Branch.

Final chlorination studies for selected OP pesticides will be conducted once analytical methods are developed with reliable identification of the OP pesticide and their oxon degradation products in chlorinated test water. These studies will be conducted using a factorial experimental design [5 sampling times x 2 replicates pesticide(s), chlorination treatments x 1 pesticide(s), non-chlorinated water treatment (control) + 1 chlorinated water (control) + 1-3 buffered water spiked with a intermediate level of parent(s) and oxon(s)].

b. Objectives

The objective is to qualitatively determine oxon formation and stability in chlorinated, laboratory water for selected OP pesticides. These data will be used in the revised cumulative OP risk assessment to characterize the potential for human exposure to oxons in treated water.

c. Glassware, Pipets, and other containers

Glassware, pipettes, and other devices used in the study should be chlorine-demand free. Soak dark or amber incubation bottles in detergent (Fisher FL-70, 4%, Fair Lawn, NJ or comparable) overnight, rinse four times with hot tap water, and then two times with distilled and deionized water. Place in 10 - 20 mg/L chlorine solution for 24 hr. After rinsing four times with distilled and deionized water and one to two times with laboratory clean water, dry in 1400 C oven overnight. Clean pipettes may need to be stored in ~ 50 mg/L Cl2 solution and rinsed three times with dosing solution before use. Store in same chlorine solution after use.

d. Materials

The following solutions will be prepared for this study:

(1) pH 6.7 borate buffer: 1.0 M boric acid [ACS grade] and 0.11 M NaOH (ACS grade) prepared in boiled laboratory reagent water;

(2) pH 8 borate buffer: 1.0 M boric acid (ACS grade) and 0.26 M NaOH (ACS grade) prepared in boiled laboratory reagent water;
(3) Chlorine solution (1000 - 3000 mg/L Cl2): Dilute reagent-grade stock solution of sodium hypochlorite (5 - 13%) with laboratory reagent water. Check the exact concentration using Standard Methods (1998) or a commercial chlorine measurement kit that can detect down to 0.1 mg/L Cl2.
(4) pH 8 hypochlorite-buffer solution: Add about 4 - 5 volume of chlorine solution (~ pH 11) to one volume of pH 6.7 borate buffer. The resulting solution gives a pH 8. About a 20% decrease in chlorine strength is expected. About 2.5 mL of this combined dosing hypochlorite-buffer solution can be added to a 1-L test water (<0.5% water sample volume change)

e.Test Waters

Fisher Environmental Grade water will be used in the water chlorination studies. Laboratory reagent water will be used for cleaning and reagent preparation.

f. Chlorine Residuals Measurement

Free chlorine residuals will be measured using a Hach pocket colorimeter analysis system and Hach Methods 8021 for free chlorine in water. This DPD method is equivalent to USEPA Method 330.5 for wastewater. It can measure free chlorine at reasonable detection limits (at least 0.1 mg/L free chlorine).

g. Preliminary and Final Study

Preliminary studies with one replication will be conducted to provide sufficient experience in measuring analytes in chlorinated water as well as an exercise in sequencing/timing the laboratory operations for the chlorination experiments. Once the preliminary studies have been conducted, final water chlorination studies will be done using two replicates for the test water. Appropriate OP pesticide and chlorine residual controls will be prepared and monitored during the chlorination tests.

h. Chlorine Dosing Study

Before the chlorination experiments are started, the chlorine demand of the test waters has to be established to determine the dose of chlorine solution that provides the target 4.0 ± 0.4 mg/L free chlorine residual. Chlorine demand of the Fisher environmental grade water will be determined. Chlorine demand is operationally defined as chlorine dose

(applied free chlorine) - free remaining chlorine residual under a specified contact or incubation period, pH and temperature. For the preliminary study, only one replicate is desirable. The unchlorinated Fisher Environmental Grade water can be used for this purpose, but it must include appropriate concentrations of co-solvents that will be used to introduce OP pesticides into solution as well as similar reaction vessels used in the experiment.

(1) Add 2 ml pH 8 borate buffer to 1 L (or proportional volumes) of unchlorinated Fisher Environmental Grade water.
(2) Check the pH. If necessary, adjust to pH 8 with dilute H2SO4 or dilute NaOH.
(3) Fill each incubation bottle (300 - 500 ml) three quarters full with the unchlorinated Fisher Environmental Grade water. Two bottles will be needed. Addition of co-solvent, in the appropriate concentration as would be employed in (I) below, may be necessary to mimic co-solvent additions through pesticide dosing procedures. The doses should be set up in duplicate to determine if the initial dosing at 4 mg/L will result in a > 1 mg/L free chlorine residual after 24 hours in the Fisher Environmental Grade water containing the co-solvents. Initial dose of 4.0 mg/L free chlorine is appropriate.
(4) Add pH 8 hypochlorite-buffer solution through a pipette held just above water surface. Dose the appropriate volume of hydrochlorite-buffer solution to give the required dose in full bottles.
(5) Cap the bottle and invert twice.
(6) Fill to top of bottle with pH 8 borate buffered unchlorinated Fisher Environmental Grade water and cap head space-free.
(7) Invert 10 times
(8) Incubate for 24 hr in the dark at room temperature.
(9) After incubation, measure the free chlorine residual, pH, and temperature. (Note: Addition of hypochlorite-buffer solution should be sequenced and timed to provide allowance for measurement of free chlorine residual and pH for each test water)
(10) The initial chlorine dose that yields an initial free chlorine residual of 4.0 ± 0.4 mg/L Cl_2 and a > 1.0 ± 0.4 mg/L at 24 hours will be selected and used in the chlorination and product stability assessment discussed below.

i. Chlorination and Product (Oxon) Stability Experiments

The study will be conducted in 4L low density polyethylene reaction vessels that can be covered with black plastic to simulate dark condition. For this final study , the chlorination experiment at pH=8 should be done in duplicate, along with one replicate OP control [test water + OP pesticides, without chlorine] , one replicate chlorine control [test water + chlorine], and one buffered water control [test water for spiking with immediate

concentrations of OPs and oxons] indicated as A1, A2, B, C, and D solutions in Table II.E-4, respectively.

i. For Treatment A:

(1) Put 2L of unchlorinated Fisher Environmental Grade water and add 4 ml of pH 8 borate buffer in a dark, 4L polyethylene reaction vessel. This will require five 4L vessels.

(2) Measure pH and adjust, if necessary, to pH 8 with dilute H2SO4 or dilute NaOH.

(3) Dose with OP pesticide(s) to achieve a concentration of 100 µg/L or below the water solubility limit, whichever is lower.

(4) Collect the unchlorinated, pesticide spiked OP sample.

(5) Add pH 8 hypochlorite-buffer solution to give an initial free chlorine residual of 4.0 ± 0.4 mg/L Cl2 and a subsequent free chlorine residual of > 1.0 ± 0.4 mg/L at 24 hours. Dose the appropriate volume of hypochlorite-buffer solution to give the required dose in the 2L sample. The time of chlorination is T = 0.

(6) Prior to taking water samples, stir solution with the aid of magnetic stirring bar for two minutes.

(7) Take samples at the time intervals for analysis summarized in Table 2:

OP pesticide – 0 (prechlorination), 1 hr, 4 hr, 24 hr, 72 hr

Transformation products (oxon, sulfoxide, sulfone, sulfone oxon, sulfoxide oxon) – 0 (prechlorination), 1 hr, 4hr, 24 hr, 72 hr

(8) The samples are immediately withdrawn from the reaction vessel and then quenched stoichiometrically with sodium thiosulfate (with slight excess) based on the free chlorine residual [1.25 mg per 100 ml aliquot]. The samples should be stored in the dark at 0 - 4°C, if they cannot be analyzed right away.

(9) Separate samples will be taken to measure the free chlorine residual, pH, and temperature.

(10) Analyze the quenched samples for the parent compound, primary product (oxon) by appropriate analytical method (GC/MS or LC/MS/MS). Other transformation products will be identified, when possible, and described as tentatively identified compounds.

ii. For Treatment B:

(1) Put 2L of unchlorinated Fisher Environmental Grade water and add 4 ml of pH 8 borate buffer in a dark, 4L polyethylene reaction vessel.

(2) Measure pH and adjust, if necessary, to pH 8 with dilute H2SO4 or dilute NaOH.

Dose with OP pesticide(s) to achieve a concentration of 100 µg/L or below the water solubility limit, whichever is lower.

(3) At approximately the same time as the collection of the chlorinated samples in Treatment A, collect the unchlorinated, pesticide spiked OP samples at 0, 1, 4, 24 and 72 hours. The samples should be stored in the dark at 0 - 4°C, if they cannot be analyzed right away.

(4) Separate samples will be taken to measure the pH and temperature.

(5) Analyze the samples for the parent compound, primary product (oxon) by appropriate analytical method (GC/MS or LC/MS/MS). Other transformation products will be identified, when possible, and described as tentatively identified compounds.

iii. For Treatment C:

(1) Put 2L of unchlorinated Fisher Environmental Grade water and add 4 ml of pH 8 borate buffer in a dark, 5L polyethylene reaction vessel.

(2) Measure pH and adjust, if necessary, to pH 8 with dilute H2SO4 or dilute NaOH.

(3) Add pH 8 hypochlorite-buffer solution to give an initial free chlorine residual of 4.0 ± 0.4 mg/L Cl2 and a subsequent free chlorine residual of > 1.0 ± 0.4 mg/L at 24 hours. Dose the appropriate volume of hypochlorite-buffer solution to give the required dose in the 2L sample.

(4) Prior to taking water samples, stir solution with the aid of magnetic stirring bar for two minutes.

(5) Collect a sample after about 1 hour for OP pesticides and for oxons.

(6) The sample is withdrawn from the reaction vessel and then quenched with the selected reducing agent (with slight excess) based on the free chlorine residual [1.25 mg per 100 ml aliquot]. The aliquots should be stored in the dark at 0 - 4° C, if they cannot be analyzed right away.

(7) A separate sample will be taken to measure the free chlorine residual, pH, and temperature at 1 hour.

(8) Analyze the sample for the parent compound, primary product (oxon) by appropriate analytical method (GC/MS or LC/MS/MS). Other transformation products will be identified, when possible, and described as tentatively identified compounds.

iv. For Treatment D:

(1) Put 2L of unchlorinated Fisher Environmental Grade water and add 4 ml of pH 8 borate buffer in a dark, 5L polyethylene reaction vessel.

(2) Measure pH and adjust, if necessary, to pH 8 with dilute H2SO4 or dilute NaOH.

(3) Collect 100 ml samples of the unchlorinated, buffered water at each sampling interval of 0, 1, 4, 24, and 72 hours.

(4) These samples will be spiked with the OP pesticide(s) and oxon(s) at a spiking level of 50 ppb, as necessary.

(6) The samples will be stored for possible analysis with sample set batches. The samples should be stored in the dark at 0-4° C, if they cannot be analyzed right away.

(7) A separate sample is taken to measure the pH and temperature.

(8) Analyze the samples for the parent compound, primary product (oxon) by appropriate analytical method (GC/MS or LC/MS/MS). Other transformation products will be identified, when possible, and described as tentatively identified compounds.

Table II.E-1.2 Proposed Sampling and Analysis Regime

Treatment Condition (Treated Water Samples and Controls: OP pesticide)	Sampling Times				
	Pre-chlorination	Postchlorination			
A1 OP Cl_2 H_2O **A2** OP Cl_2 H_2O	0	1 hr	4 hrs	24 hrs	72 hrs
	OP	OP	OP	OP	OP
	Oxon[1]	Oxon	Oxon	Oxon	Oxon
		Cl	Cl	Cl	Cl
B OP H2O	OP	OP	OP	OP	OP
	Oxon	Oxon	Oxon	Oxon	Oxon
C Cl2 H2O		OP			
		Oxon			
		Cl			
D H_2O	Spiked OP	Spiked OP	Spiked OP	Spiked OP	Spiked OP
	Spiked Oxon	Spiked Oxon	Spiked Oxon	Spiked Oxon	Spiked Oxon

1- Sulfone, sulfoxide, sulfone oxon, and sulfoxide oxon will be analyzed if appropriate for the test pesticide. This assumes analytical methods and analytical standards are available for the various degradation products.

j. Data Reduction and Reporting

Report detections of parent OP and its degradation products. Calculate concentrations, when possible, of OP pesticides and their stability products. Report identities and structural formulas of transformation products.

k. Interpretation of Results

The interpretation of study results will be dependent on the detection of oxon degradation products in the chlorinated test water treatments. The control treatments will be used to assess whether the OP pesticide undergoes oxidation in non-chlorinated test water and to assess whether OP pesticide or its degradation products are in the chlorinated water without pesticide dosing. Because the experimental design has minimal replication and the analytical methods are not fully vetted for all the OP pesticides and their oxon degradation products, there will be strict qualitative interpretation on whether OP pesticides undergo oxidative desulfonation during a 72 hour contact time in chlorinated laboratory water.

This deduction will be reached if oxons are detected in either replication in the chlorinated laboratory water treatments at any sampling time and the OP pesticide is stable in non-chlorinated laboratory water. Additionally, the detection of oxons in chlorinated water at the 24 hour or 72 hour sampling times will suggest the oxon is stable enough in chlorinated water to have the potential for dietary exposure through drinking water.

l. References

Magara, Y. et al., 1994. Degradation of pesticides by chlorination during water purification. Water Sci. Technol. 30(7): 119-128.

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9. Appendix 2: Results of Analyses of OP Pesticides and Oxons in the Water Chlorination Studies

Table II.E-1.3 Results of the GC-MSD Analyses of OP Pesticides and Oxons in the Water Chlorination Studies - ECB

OP	Time, hrs	Parent OP				Oxon			
		A1	A2	B	D-spike[2]	A1	A2	B	D-spike[2]
Methidathion	0	106	64	107	51	ND	ND	ND	48
	1	ND	ND	110	NA	90	98	ND	NA
	4	ND	ND	109	47	81	97	ND	47
	24	ND	ND	103	NA	72	77	ND	NA
	72	ND	ND	101	59	66	67	ND	59
Methyl parathion	0	95	94	96	47	ND	ND	ND	48
	1	12	ND	89	NA	90	69	ND	NA
	4	ND	ND	98	46	72	85	ND	47
	24	ND	ND	83	NA	66	70	ND	NA
	72	ND	ND	88	53	68	66	ND	59
Phosmet	0	80	81	81	20	ND	ND	ND	20
	1	ND	ND	103	NA	57	69	ND	NA
	4	ND	ND	17	2	7	9	ND	2
	24	ND	ND	ND	NA	ND	ND	ND	NA
	72	ND	ND	ND	49	ND	ND	ND	43
Phorate	0	62	61	62	38	ND	ND	ND	38
	1	ND	ND	68	NA	ND	ND	ND	NA
	4	ND	ND	52	25	ND	ND	ND	32
	24	ND	ND	17	NA	ND	ND	ND	NA
	72	ND	ND	11	45	ND	ND	ND	45
Bensulide[1]	0	NA	NA	NA	NA	NA	NA	NA	NA
	1	NA	NA	NA	NA	NA	NA	NA	NA
	4	NA	NA	NA	NA	NA	NA	NA	NA
	24	NA	NA	NA	NA	NA	NA	NA	NA
	72	NA	NA	NA	NA	NA	NA	NA	NA
Chlorethoxy-fos	0	41	43	41	29	ND	ND	ND	39
	1	12	12	42	NA	26	30	ND	NA
	4	ND	ND	32	26	41	55	ND	38
	24	ND	ND	3	NA	26	30	ND	NA
	72	ND	ND	ND	51	23	23	ND	54
Disulfoton	0	64	64	64	36	ND	ND	ND	40
	1	ND	ND	68	NA	ND	ND	ND	NA
	4	ND	ND	56	34	ND	ND	ND	37
	24	ND	ND	24	NA	ND	ND	ND	NA
	72	ND	ND	16	45	ND	ND	ND	48
Terbufos	0	63	63	65	39	ND	ND	ND	38
	1	ND	ND	64	NA	ND	ND	ND	NA

OP	Time, hrs	Parent OP				Oxon			
		A1	A2	B	D-spike[2]	A1	A2	B	D-spike[2]
	4	ND	ND	46	34	ND	ND	ND	31
	24	ND	ND	9	NA	ND	ND	ND	NA
	72	ND	ND	ND	49	ND	ND	ND	46
Phostebupirim	0	79	79	78	41	ND	ND	ND	44
	1	2	2	71	NA	44	43	ND	NA
	4	ND	ND	65	42	42	50	ND	43
	24	ND	ND	30	NA	44	43	ND	NA
	72	ND	ND	14	51	47	50	ND	52
Temephos[3]	0	93	94	94	50	NA	NA	NA	NA
	1	ND	ND	121	NA	NA[3]	NA	NA	NA
	4	ND	ND	93	41	NA	NA	NA	NA
	24	ND	ND	43	NA	NA	NA	NA	NA
	72	ND	ND	11	50	NA	NA	NA	NA

[1] Bensulide is not suitable for the current GC-MSD conditions
[2] Only the D-Spike Samples at 0, 4, and 72 hours were analyzed.
[3] Temephos oxon standard is not available.

Table II.E-1.4 Results of the LC/MS/MS Analyses of OP Pesticides and Oxons in the Water Chlorination Studies - ACB

OP	Time, hrs	Parent OP				Oxon			
		A1	A2	B	D-spike[1]	A1	A2	B	D-spike[1]
Methidathion	0	67	64	72	39	ND	ND	ND	44
	1	ND	ND	73	44	80	81	ND	48
	4	ND	ND	73	45	87	81	ND	50
	24	ND	ND	74	47	80	76	ND	51
	72	ND	ND	77	NA	58	50	ND	NA
Methyl parathion[2]	0	NA	NA	NA	NA	ND	ND	ND	52
	1	NA	NA	NA	NA	58	46	ND	53
	4	NA	NA	NA	NA	79	72	ND	55
	24	NA	NA	NA	NA	81	72	ND	58
	72	NA	NA	NA	NA	78	75	ND	NA
Phosmet[3]	0	NA	NA	NA	NA	NA	NA	NA	NA
	1	NA	NA	NA	NA	NA	NA	NA	NA
	4	NA	NA	NA	NA	NA	NA	NA	NA
	24	NA	NA	NA	NA	NA	NA	NA	NA
	72	NA	NA	NA	NA	NA	NA	NA	NA
Phorate	0	22	23	26	18	ND	ND	ND	45
	1	ND	ND	24	19	ND	ND	ND	43
	4	ND	ND	20	18	ND	ND	ND	45
	24	ND	ND	11	22	ND	ND	ND	50
	72	ND	ND	8	NA	ND	ND	ND	NA

OP	Time, hrs	Parent OP				Oxon			
		A1	A2	B	D-spike[1]	A1	A2	B	D-spike[1]
Bensulide[1]	0	15	15	18	14	ND	ND	ND	43
	1	2	2	21	15	58	57	ND	44
	4	2	3	16	14	57	52	ND	46
	24	ND	ND	15	15	55	49	ND	48
	72	ND	ND	17	NA	60	56	ND	NA
Chlorethoxy-fos[2]	0	NA	NA	NA	NA	ND	ND	ND	40
	1	NA	NA	NA	NA	17	15	ND	38
	4	NA	NA	NA	NA	25	23	ND	38
	24	NA	NA	NA	NA	24	20	ND	40
	72	NA	NA	NA	NA	17	13	ND	NA
Disulfoton	0	ND	ND	ND	10	ND	ND	ND	49
	1	ND	ND	ND	9	ND	ND	ND	47
	4	ND	ND	ND	10	ND	ND	ND	50
	24	ND	ND	ND	11	ND	ND	ND	51
	72	ND	ND	ND	NA	ND	ND	ND	NA
Terbufos	0	11	11	13	11	ND	ND	ND	33
	1	ND	ND	12	11	ND	ND	ND	30
	4	ND	ND	8	11	ND	ND	ND	32
	24	ND	ND	3	12	ND	ND	ND	39
	72	ND	ND	6	NA	ND	ND	ND	NA
Phostebupirim	0	19	19	23	18	ND	ND	ND	48
	1	2	3	22	17	49	ND	ND	48
	4	1	1	14	18	55	51	ND	48
	24	ND	ND	8	18	59	54	ND	51
	72	ND	ND	10	NA	56	52	ND	NA
Temephos[4]	0	55	54	67	10	NA[4]	NA	NA	NA
	1	3	3	46	9	NA	NA	NA	NA
	4	3	3	49	9	NA	NA	NA	NA
	24	ND	ND	40	10	NA	NA	NA	NA
	72	ND	ND	NA	NA	NA	NA	NA	NA

[1] Sample D-spike 72 hr was not included
[2] Methyl parathion and chloroethoxyfos are not suitable for the current LC/MS conditions
[3] only traces remained after 24 hr.
[4] Temephos oxon standard is not available.

E-2. OP Cumulative Exposure in Drinking Water: The Effects of Water Chlorination on Three Specific Organophosphate (OP) Pesticides (Phase II)

This report is an addendum to the 2002 OP CRA drinking water appendix III.E.4 – Effects of Drinking Water Treatment on Organophosphate Pesticides. Phase I of this study evaluated the potential of ten OP pesticides to form oxons as a result oxidation during drinking water treatment processes. Phase II of the study evaluated the potential of the sulfone and sulfoxide transformation products of disulfoton, phorate, and terbufos to form oxons.

The studies were conducted by the USEPA Office of Pesticide Program (OPP) Biological and Economic Analysis Division (BEAD) laboratories and have been reviewed by the USEPA Office of Research and Development (ORD). The results support the oxon characterization in the drinking water exposure assessment for the 2006 OP CRA.

1. Executive Summary – Phase II

Three organophosphate (OP) pesticides [phorate, disulfoton, terbufos] were evaluated for their potential to undergo oxidation to their respective oxidative products [oxons, sulfoxides, sulfoxide oxons, sulfones, and sulfone oxons] in laboratory water simulating the chlorination process in drinking water facilities over a 72 hour exposure period. Samples were collected after 0, 0.25, 4, 24, and 72 hours of chlorination and analyzed by both gas chromatography-mass selective detection (GC-MSD) and liquid chromatography-tandem mass spectrometry (LC/MS/MS) to determine the presence of the pesticides and their oxidative products. The data obtained supplement previous data obtained on a more extensive group of organophosphate pesticides (Phase I).

The results of the Phase II Experiment confirm the results of the Phase I Experiment in that these three OP pesticides [phorate, disulfoton, terbufos] are unstable and degraded in unchlorinated buffered laboratory water over the 72 hour exposure period. In addition, as in the Phase I experiments, phorate, disulfoton, and terbufos did not undergo oxidation to their oxons upon chlorination under the experiment conditions.

However, in the current experiment, it was determined that two of the OP pesticides [phorate and disulfoton] underwent oxidation to other oxidation products [sulfone oxons]. The phorate sulfone oxon was detected at the 4 and 24 sampling times at trace concentrations (detection limit) and was not detected at the 72 hours. The disulfoton sulfone oxon was detected at the 0.25 hour sampling time in significant concentrations which increased at 4 hours, and then gradually decreased during the 72 hour exposure

period. This oxidative product was present at both the 24 and 72 hour sampling times.

In the first four hours of the experiment, significant amounts of the sulfoxide oxons of the three OP pesticides were detected; however, they were not stable for more than 4 hours, which suggests that the sulfoxide oxons are one of the intermediate oxidation products to the sulfone oxons.

Re-examination of the gas chromatographic/mass spectrometric chromatograms (GC-MSD) of the Phase I Experiment reveals the presence of these same oxidative products at approximately the same exposure periods and further confirms the findings of the Phase II Experiment.

Table II.E-2.1 Results for pesticides and oxidation products examined in study.

OP Pesticide	Parent OP			Sulfoxide Oxon		Sulfone Oxon	
	Stability in water over 72 hrs (no chlorin-ation)	Oxon formation after 1 hr (upon chlorin-ation)	Oxon stability after 72 hrs	Forma-tion after 1 hr	Stability after 72 hrs	Forma-tion after 1 hr	Stabili ty after 72 hrs
Phorate	Poor	None	-	Yes	No	Yes	No
Disulfoton	Poor	None	-	Yes	No	Yes	Yes
Terbufos	Poor	None	-	Yes	No	No	-

In accordance with the Quality Assurance Project Plan (QAPP) for this phase of the study, there were two elements necessary for the strict qualitative interpretation whether the three OP pesticides underwent oxidative desulfonation during a 72 hour contact time in chlorinated laboratory water. This conclusion would be reached if the oxidative products are detected at any quantifiable level in either replication in the chlorinated laboratory water treatments at any sampling time and the OP pesticides are stable in non-chlorinated laboratory water. Because none of the parent OPs were stable in non-chlorinated water, none of the three pesticides met those criteria.

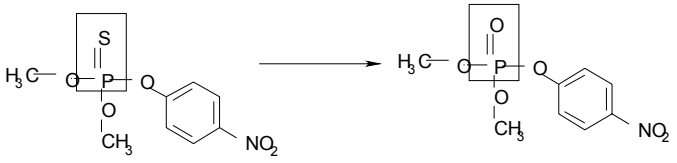
2. Introduction

The application of pesticides in arable lands has resulted in the contamination of natural waters such as surface water and groundwater. The initial contamination at the application sites has spread via surface runoff to nearby lakes, rivers, and streams and through subsurface transport to aquifers. The contaminated surface waters and ground waters are eventually used as source or raw waters in some community drinking water systems. After subjecting the raw water to different treatment processes in the water purification facilities, the concentrations of the

pesticides may change or remain essentially the same in the treated or final drinking water. Studies conducted by scientists at EPA's ORD in Cincinnati (Miltner et al, 1989) indicate that conventional treatment (coagulation/clarification, filtration, softening, recarbonation, and chlorination) are generally not effective in removing certain pesticides from raw water. However, other pesticides are unstable in the presence of chemical disinfectant such as chlorine.

Previous studies in Japan (Magara et al, 1994) and United States (Tierney et al, 2001; Duirk and Collette, 2006) indicate that certain organophosphate pesticides can be transformed to their oxons during chemical disinfection by chlorine compounds. This chemical transformation process is shown in Figure II.E.2 1.

Figure II.E-2.1 Oxidative Desulfonation Reaction of an Organophosphate Pesticide in Chlorinated Water.



This transformation is a concern because chlorination is the most commonly used disinfection technique in many US drinking water treatment plants and the product oxons are generally considered to be more toxic than the parent compounds.

The Food Quality Protection Act of 1996 (FQPA) requires that all chemical pesticide residues in or on food be examined for any possible adverse health effects through exposure. Drinking water is one of the pathways for dietary exposure. Five organophosphate pesticides (diazinon, chlorpyrifos, methidathion, methyl parathion, and malathion) have been examined and have been found to transform during chlorination into their associated oxons. Three specific organophosphate pesticides [phorate, disulfoton, and terbufos] have other known oxidative products [sulfoxides, sulfoxide oxons, sulfones, and sulfone oxons] for which there is little or no data on their potential for oxidative transformation during these conditions. Consequently, data and additional information are needed on the probable oxidation of these organophosphate pesticides and the relative stability of oxidative products in chlorinated water. The three organophosphate pesticides and their degradation products considered in this study are listed in Table II.E-2.2.

Table II.E-2.2 Selected Organophosphate Pesticides from the Cumulative OP Assessment without Water Treatment Data on Chlorination Effects on Oxon Formation

OP Parent	OP Degradation Products
Phorate	phorate oxon phorate sulfoxide phorate sulfone phorate sulfoxide oxon phorate sulfone oxon
Disulfoton	disulfoton oxon disulfoton sulfoxide disulfoton sulfone disulfoton sulfoxide oxon disulfoton sulfone oxon
Terbufos	terbufos oxon terbufos sulfoxide terbufos sulfone terbufos sulfoxide oxon terbufos sulfone oxon

The objective of this study is to provide a qualitative screening level assessment on the potential for oxidation product formations in chlorinated laboratory water and the stability of the selected organophosphate pesticides in both un-chlorinated and chlorinated water and the stability of their respective oxidation products in the chlorinated laboratory water. There were approximately twenty organophosphate pesticides considered in the cumulative OP risk assessment. The three selected pesticides being tested in this study consist of the pesticides, which are capable of forming multiple oxidation products, have outdoor use patterns, and have no chlorination water treatment data available. These data will be used in the revised cumulative OP risk assessment to characterize the potential for human exposure to oxons in treated water.

3. Project Description

The project description is listed in the study protocol in Appendix 1 (Section 7). A brief summary description follows:

For each of the ten OP pesticides to be tested, the experimental design consisted of:

- One replicate OP control [test water + OP pesticide, without chlorine]
- One replicate chlorine control [test water + chlorine]
- Two replicates of treatment [OP pesticide + test water + chlorine]
- One buffered water sample spiked with the ten pesticides and nine oxons at a concentration of ½ of the spiking concentration (50 ppb) at each sampling time.

Chlorination experiments will be conducted in Fisher Environmental Grade reagent water to eliminate chlorine demand considerations. Similar testing conditions using laboratory waters are recommended as screening level testing for CCL water treatment studies and pesticide treatment studies at ORD. The chlorine dose in the laboratory water will be equivalent to the recommended maximum disinfectant residual (RMDL) of 4 mg/L free chlorine concentration ± 10%. The pH of the Fisher reagent water will be adjusted to pH 8 to represent typical water treatment conditions. The experiment will be conducted for 72 hours with sampling times immediately prior to chlorination (~2 minutes before pesticide dosing), 0.25 hour, 4 hours, 24 hours, and 72 hours post chlorination. The 24 and 72 hour sampling times were selected to represent the treatment system water residence and/or distribution transport times of approximately 24 hr or longer. The pesticide concentration in the experiment will be 100 ppb or below the solubility limit of the pesticide whichever is lower. The experiments will be conducted using a mixture of the OP pesticides delivered to the system with low co-solvent concentrations or in the absence of co-solvents. The chlorine demand from co-solvents and degradation processes will be determined by measuring free chlorine at each sampling interval.

4. Method and Materials

Fisher Scientific Certified Environmental Grade water was used as the test water. Water quality parameters of the test water were:

Test	Value	Unit
Color	< 5	APHA
Residue after Evaporation	< 1	ppm
Fluorescence (as quinine)	< 100	ppt
Resistivity	> 18	MΩ
Total Organic Carbon	< 20	ppb

Water samples must be labeled clearly, and should include date, time, and name of the preparer(s). To preserve the integrity of the data, all samples must be stored at ~ 4^{o}C until extraction to minimize the physicochemical changes in the samples. If sample extraction into a solvent is necessary, extracts must be stored below 0^{o}C and also analyzed as soon as possible. All samples used and generated during the study should be properly disposed of.

Quality assurance samples shall consist of:
1) reagent water blank – analysis of reagent water (one time only);
2) method blank – analysis of buffered reagent water plus chlorine; [Carboy C, Table 1]; (time 0.25 hr);

3) non-chlorinated degradation check – analysis of buffered reagent water plus OPs [Carboy B, Table 2]; (time 0, 0.25, 4, 24, and 72 hrs);
4) matrix water blank – analysis of buffered reagent water (time 0);
5) matrix water spike – analysis of buffered reagent water plus 50 ppb of the OP parent(s) plus 50 ppb oxon(s) (one spike per analytical sample set).

These measures are classified as critical measurements and should be prepared and analyzed with each group of samples to monitor laboratory contamination and method performance. Addition of surrogate compounds to environmental samples is also recommended to measure the efficiency of the method. The surrogate compounds should not be normally found in the environment and should be selected such that the interference with elution of target analytes and the effect from sample matrix are minimal.

a. Analytical Procedures

The analytical procedures used should be able to accurately identify and measure the presence of the target analytes in the samples. Identification and quantitation of residues will be by gas chromatography-mass selective detection (GC/MSD) and/or liquid chromatography/tandem mass spectrometry (LC/MS/MS) techniques.

A calibration curve will be constructed with mixtures(s) of pure standards (target analytes) at concentrations that range from twice the spiking level to the method detection limit. Complete initial calibration curves shall be prepared monthly, and the individual calibration standards verified each day of operation.

In some cases, the analytical procedures may not be completely developed to allow for complete quantification of the parent OP and its degradation products. Nevertheless, the analytical method should be capable of providing clear separation of known pesticide residues on chromatograms to allow for residue identification.

b. Test Protocol

These studies will be conducted at the OPP/BEAD/ACB Fort Meade and OPP/BEAD/ECB Stennis Space Center laboratories. A complete description of testing protocol can be found in the Appendix 1 (Section 7). Final studies will not be conducted for compounds unless the analytical method has been shown to be capable of detecting of the parent compounds and their oxons in chlorinated water during the preliminary testing stage.

The control treatments will be used to assess whether the OP pesticide undergoes oxidation in non-chlorinated laboratory water and to assess whether OP pesticide or its oxidation products are in the chlorinated water without pesticide dosing. Because the experimental design has minimal replication and the analytical methods are not fully vetted for all the OP pesticides and their oxidation products, there will be strict qualitative interpretation (i.e. presence or absence of oxidation product) on whether OP pesticides [phorate, disulfoton, and terbufos] undergo oxidative desulfonation during a 72 hour contact time in chlorinated laboratory water. This deduction will be reached if their oxidation products [sulfoxides and sulfones and their associated sulfoxide and sulfone oxons] are detected at any quantifiable level in either replication in the chlorinated laboratory water treatments at any sampling time and the OP pesticide is stable in non-chlorinated laboratory water. Additionally, the detection of oxidation products in chlorinated water at the 24 hour or 72 hour sampling times will suggest the oxidation product is stable enough in chlorinated water to have the potential for dietary exposure through drinking water.

c. Assessment and Oversight

A QA/QC laboratory audit will be performed at the conclusion of the water chlorination studies with OP pesticides and their sulfone, sulfoxide, sulfone oxon, and sulfoxide oxon.

5. Results

a. The Formation of Oxidation Products from the Three OP Pesticides in Chlorinated Water

Three organophosphate (OP) pesticides [phorate, disulfoton, terbufos] were evaluated for their potential to undergo oxidation to their respective oxidation products in laboratory water simulating the chlorination process in drinking water facilities. In these studies, the OP pesticides were dissolved into pH 8.0 buffered water and then chlorinated with a sodium hypochlorite solution. Over a 72 hour exposure period, water samples were collected, processed, and analyzed by both gas chromatography-mass selective detection (GC-MSD) and liquid chromatography-tandem mass spectrometry (LC/MS/MS) to determine the presence of the pesticides and their oxons. The results are presented in Appendix 2 for both the GS-MSD and LC/MS/MS studies.

The results of both studies (GC-MSD & LC/MS/MS) showed that the three OP pesticides (phorate, disulfoton, and terbufos) did not undergo oxidation into their oxons under the experiment conditions.

Two of the twelve remaining oxidation products [phorate sulfone oxon and disulfoton sulfone oxon] formed stable compounds over the 24 exposure period, but only the disulfoton sulfone oxon was present at 72 hours. The phorate sulfone oxon was present at trace concentration at the minimum detection limit; the disulfoton sulfone oxon was present at higher concentrations. In the first four hours of the experiment, phorate sulfoxide oxon, disulfoton sulfoxide oxon, and terbufos sulfoxide oxon were detected; however, they were unstable and disulfoton sulfoxide oxon was not detected at the 4 hour exposure time and phorate sulfoxide oxon and terbufos sulfoxide oxon were not detected at the 24 hour exposure time.

A re-examination of the full scan of the gas chromatographic/mass spectrometric (GC-MSD) chromatograms from the Phase I Experiment confirmed these findings.

The analytical methods of GC-MSD and LC/MS/MS were complimentary in the detection of the three OP pesticide parents and the majority of their oxidation products. The current GC/MSD conditions were not suitable for the detection of phorate sulfoxide, phorate sulfoxide oxon, terbufos sulfoxide, and terbufos sulfoxide oxon; however, the LC/MS/MS conditions were suitable for all 18 compounds in the study.

b. The Stability of Three OP Pesticides in Unchlorinated Water

The three organophosphate (OP) pesticides [phorate, disulfoton, terbufos] were evaluated in buffered laboratory water to act as a control to the separate studies of the pesticides in the buffered water during the chlorination process. In these studies the OP pesticides were dissolved into a pH 8.0 buffered water. Over a 72 hour exposure period, water samples were collected, processed, and analyzed by both gas chromatography-mass selective detection (GC-MSD) and liquid chromatography-tandem mass spectrometry (LC/MS/MS) to determine the presence of the pesticides and their oxons without chlorination. The results are presented in Appendix 2 for both the GS-MSD and LC/MS/MS studies.

The results demonstrated and confirm that the three OP pesticides [phorate, disulfoton, and terbufos] are unstable and degrade in the buffered water without chlorination over the 72 hour exposure period. Trace concentrations of disulfoton sulfoxide were detected at the minimum detection limit.

A re-examination of the full scan of the gas chromatographic/mass spectrometric (GC-MSD) chromatograms from the Phase I Experiment confirmed these findings.

c. The Stability of Free Chlorine Concentrations in Water

The concentration of chlorine as free chlorine was evaluated in buffered laboratory water to act as a control to the separate studies of the pesticides in the buffered water during the chlorination process. In these studies chlorine as free chlorine was added to a pH 8.0 buffered water. Over a 72 hour exposure period, water samples were collected and analyzed to determine the stable concentration of this form of chlorine. In both studies the concentration of free chlorine remained stable within 25% of the initial concentration and neither the OP pesticides nor their oxidation products were detected at any time during the 72 hour exposure period.

d. The Stability of the Three OP Pesticides and Their Oxidation Products as Laboratory Control Spike Samples

Three organophosphate (OP) pesticides [phorate, disulfoton, terbufos] and their fifteen available oxidation products (Table 1) were spiked into pH 8.0 buffered laboratory water to act as laboratory control spike samples. These samples were used to assess the method performance of the course of the study. The water samples were collected, spiked, processed, and analyzed by both gas chromatography-mass selective detection (GC-MSD) and liquid chromatography-tandem mass spectrometry (LC/MS/MS) to determine the concentration of the pesticides and their oxidation products. The results are presented in Appendix 2 for both the GS-MSD and LC/MS/MS studies.

6. Summary

There were two elements necessary to the **strict qualitative interpretation** whether these three OP pesticides underwent oxidative desulfonation during a 72 hour contact time in chlorinated laboratory water. This conclusion could be reached if:

1) The oxidation products of the three OP pesticides are detected at any quantifiable level in either replication in the chlorinated laboratory water treatments at any sampling time.

- There were five quantifiable oxidation products detected in the chlorinated laboratory water during the seventy two hour exposure period [phorate sulfoxide oxon, phorate sulfone oxon, disulfoton

sulfoxide oxon, disulfoton sulfone oxon, and terbufos sulfoxide oxon].

and

2) The OP pesticides are stable in non-chlorinated laboratory water.
   - o All three OP pesticides were unstable and degraded in the unchlorinated laboratory water.

3) Additionally, there were detection of oxidation products in chlorinated water at the 24 hour or 72 hour sampling times would suggest the oxidation product is stable enough in chlorinated water to have the potential for dietary exposure through drinking water.
   - o One of the oxidation products [phorate sulfone oxon] was stable at trace levels at the 24 hour sampling time and one of the oxidation products [disulfoton sulfone oxon] was stable at both the 24 and 72 hour sampling times.

None of the three parent OP pesticides meet the criteria as established in the QAPP to conclude that they underwent oxidative desulfonation into their respective oxons. However, it should be noted that two of the parents [phorate and disulfoton] underwent oxidative desulfonation to phorate sulfone oxon and disulfoton sulfone oxon.

7. References

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USEPA, Laboratory Study on the Effects of Chlorinated Water on OP Pesticides, Quality Assurance Project Plan, OPP/EFED/WTEWG, April 24, 2006.

USEPA, Laboratory Study on the Effects of Chlorinated Water on OP Pesticides, Final Report, OPP/EFED/WTEWG, May 15, 2006.

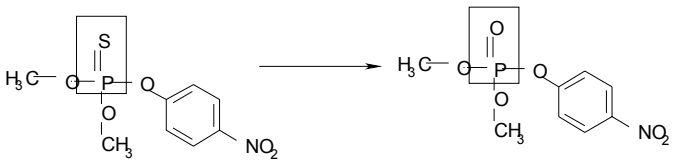
8. Appendix 1: Procedures for the Preliminary Laboratory Study on the Effects of Chlorinated Water on OP Pesticides, Phase II

This appendix was prepared by the Water Treatment Effects Workgroup, Environmental Fate and Effects Division of the USEPA Office of Pesticide Programs on June 8, 2006.

a. Introduction

Previous studies in Japan (Magara et al, 1994) and United States (Tierney et al, 2001) indicate that certain organophosphate pesticides can be transformed during disinfection by chlorine compounds to oxons. This chemical transformation process is shown in Figure II.E.2 2.

Figure II.E-2.2 Oxidative Desulfonation Reaction of an Organophosphate Pesticide in Chlorinated Water.



This transformation is a concern because chlorination is widely used in many drinking water treatment plants and the product oxons are generally considered to be more toxic than the parent compounds. Consequently, data and additional information are needed on the probable oxidation of selected organophosphate pesticides and the relative stability of oxons in chlorinated water. In the Laboratory Study on the Effects of Chlorinated Water on OP Pesticides, Phase I, ten organophosphate (OP) pesticides were examined and it was determined that five OP pesticides [methidathion, bensulide, chlorethyoxyfos, methyl parathion, and phostebupirim] formed stable oxons in chlorinated water. However, three of those pesticides [phorate, disulfoton, and terbufos] have additional oxidation products [sulfoxides, sulfoxide oxons, sulfones, and sulfone oxons] that can be formed. The organophosphate pesticides and their oxidation products considered in this testing protocol are listed in Table II.E.2 3.

Table II.E-2.3 Selected Organophosphate Pesticides from the Cumulative OP Assessment without Water Treatment Data on Chlorination Effects on Oxon Formation

OP Parent	OP Degradation Products
Phorate	phorate oxon phorate sulfoxide phorate sulfone phorate sulfoxide oxon phorate sulfone oxon
Disulfoton	disulfoton oxon disulfoton sulfoxide disulfoton sulfone disulfoton sulfoxide oxon disulfoton sulfone oxon
Terbufos	terbufos oxon terbufos sulfoxide terbufos sulfone terbufos sulfoxide oxon terbufos sulfone oxon

Chlorination experiments will be conducted in Fisher certified environmental grade test water. Although the experiments will be conducted in environmental grade water, water pH (pH=8) will be altered to represent water treatment plant conditions. The chlorine dose in the laboratory water will be equivalent to the recommended maximum disinfectant residual (RMDL) of 4 mg/L free chlorine. Because the laboratory water will have extremely low chlorine demand, the free chlorine concentration and total chlorine concentration should be similar. The pH of the laboratory water will be adjusted to pH 8 to represent typical water treatment conditions. The experiment will be conducted for 72 hours with sampling times immediately prior to chlorination and 0.25 hour, 4 hours, 24 hours, and 72 hours post chlorination. The 24 and 72 hour sampling times were selected to represent the treatment system water residence and/or distribution transport times of approximately 24 hr or longer. The pesticide concentration in the experiment will be 100 □g/L or below the solubility limit of the pesticide whichever is lower. The experiments will be conducted using a mixture of the OP pesticides. The experiments will be conducted with low co-solvent concentrations or in the absence of co-solvents. The chlorine demand from co-solvents and degradation processes will be determined by measuring free chlorine at each sampling interval.

The experimental plan will consist of a series of preliminary studies and final studies. These studies will be conducted by EPA personnel at the Biological and Economic Analysis Division Fort Meade Analytical Laboratory and Stennis Space Center Environmental

Chemistry Laboratory. The chlorination study protocol and QAPP will be reviewed by Richard Miltner, P.E. from the ORD/NRMRL/Water Supply and Water Resources Division/ Treatment Technology Evaluation Branch.

Final chlorination studies for selected OP pesticides will be conducted once analytical methods are developed with reliable identification of the OP pesticide and their oxon degradation products in chlorinated test water. These studies will be conducted using a factorial experimental design [5 sampling times x 2 replicates pesticide(s), chlorination treatments x 1 pesticide(s), non-chlorinated water treatment (control) + 1 chlorinated water (control) + 1-3 buffered water spiked with a intermediate level of parent(s) and oxon(s)].

b. Objectives

The objective is to qualitatively determine oxon formation and stability in chlorinated, laboratory water for selected OP pesticides. These data will be used in the revised cumulative OP risk assessment to characterize the potential for human exposure to oxons in treated water.

c. Glassware, Pipets, and other containers

Glassware, pipettes, and other devices used in the study should be chlorine-demand free. Soak dark or amber incubation bottles in detergent (Fisher FL-70, 4%, Fair Lawn, NJ or comparable) overnight, rinse four times with hot tap water, and then two times with distilled and deionized water. Place in 10 - 20 mg/L chlorine solution for 24 hr. After rinsing four times with distilled and deionized water and one to two times with laboratory clean water, dry in 1400 C oven overnight. Clean pipettes may need to be stored in ~ 50 mg/L Cl2 solution and rinsed three times with dosing solution before use. Store in same chlorine solution after use.

d. Materials

The following solutions will be prepared for this study:

(5) pH 6.7 borate buffer: 1.0 M boric acid [ACS grade] and 0.11 M NaOH (ACS grade) prepared in boiled laboratory reagent water;
(6) pH 8 borate buffer: 1.0 M boric acid (ACS grade) and 0.26 M NaOH (ACS grade) prepared in boiled laboratory reagent water;
(7) Chlorine solution (1000 - 3000 mg/L Cl2): Dilute reagent-grade stock solution of sodium hypochlorite (5 - 13%) with laboratory reagent water. Check the exact concentration using Standard Methods (1998)

or a commercial chlorine measurement kit that can detect down to 0.1 mg/L Cl2.

(8) pH 8 hypochlorite-buffer solution: Add about 4 - 5 volume of chlorine solution (~ pH 11) to one volume of pH 6.7 borate buffer. The resulting solution gives a pH 8. About a 20% decrease in chlorine strength is expected. About 2.5 mL of this combined dosing hypochlorite-buffer solution can be added to a 1-L test water (<0.5% water sample volume change)

e. Test Waters

Fisher Environmental Grade water will be used in the water chlorination studies. Laboratory reagent water will be used for cleaning and reagent preparation.

f. Chlorine Residuals Measurement

Free chlorine residuals will be measured using a Hach pocket colorimeter analysis system and Hach Methods 8021 for free chlorine in water. This DPD method is equivalent to USEPA Method 330.5 for wastewater. It can measure free chlorine at reasonable detection limits (at least 0.1 mg/L free chlorine).

g. Preliminary and Final Study

Preliminary studies with one replication will be conducted to provide sufficient experience in measuring analytes in chlorinated water as well as an exercise in sequencing/timing the laboratory operations for the chlorination experiments. Once the preliminary studies have been conducted, final water chlorination studies will be done using two replicates for the test water. Appropriate OP pesticide and chlorine residual controls will be prepared and monitored during the chlorination tests.

h. Chlorine Dosing Study

Before the chlorination experiments are started, the chlorine demand of the test waters has to be established to determine the dose of chlorine solution that provides the target 4.0 ± 0.4 mg/L free chlorine residual. Chlorine demand of the Fisher environmental grade water will be determined. Chlorine demand is operationally defined as chlorine dose (applied free chlorine) - free remaining chlorine residual under a specified contact or incubation period, pH and temperature. For the preliminary study, only one replicate is desirable. The unchlorinated Fisher Environmental Grade water can be used for this purpose, but it must include appropriate concentrations of co-solvents

that will be used to introduce OP pesticides into solution as well as similar reaction vessels used in the experiment.

1. Add 2 ml pH 8 borate buffer to 1 L (or proportional volumes) of unchlorinated Fisher Environmental Grade water.
2. Check the pH. If necessary, adjust to pH 8 with dilute H_2SO_4 or dilute NaOH.
3. Fill each incubation bottle (300 - 500 ml) three quarters full with the unchlorinated Fisher Environmental Grade water. Two bottles will be needed. Addition of co-solvent, in the appropriate concentration as would be employed in (I) below, may be necessary to mimic co-solvent additions through pesticide dosing procedures. The doses should be set up in duplicate to determine if the initial dosing at 4 mg/L will result in a > 1 mg/L free chlorine residual after 24 hours in the Fisher Environmental Grade water containing the co-solvents. Initial dose of 4.0 mg/L free chlorine is appropriate.
4. Add pH 8 hypochlorite-buffer solution through a pipette held just above water surface. Dose the appropriate volume of hydrochlorite-buffer solution to give the required dose in full bottles.
5. Cap the bottle and invert twice.
6. Fill to top of bottle with pH 8 borate buffered unchlorinated Fisher Environmental Grade water and cap head space-free.
7. Invert 10 times
8. Incubate for 24 hr in the dark at room temperature.
9. After incubation, measure the free chlorine residual, pH, and temperature. (Note: Addition of hypochlorite-buffer solution should be sequenced and timed to provide allowance for measurement of free chlorine residual and pH for each test water)
10. The initial chlorine dose that yields an initial free chlorine residual of 4.0 ± 0.4 mg/L Cl_2 and a > 1.0 ± 0.4 mg/L at 24 hours will be selected and used in the chlorination and product stability assessment discussed below.

i. Chlorination and Product (Oxon) Stability Experiments

The study will be conducted in 4L low density polyethylene reaction vessels that can be covered with black plastic to simulate dark condition. For this final study , the chlorination experiment at pH=8 should be done in duplicate, along with one replicate OP control [test water + OP pesticides, without chlorine] , one replicate chlorine control [test water + chlorine], and one buffered water control [test water for spiking with

immediate concentrations of OPs and oxons] indicated as A1, A2, B, C, and D solutions in Table II.E-4, respectively.

i. For Treatment A:

(1) Put 2L of unchlorinated Fisher Environmental Grade water and add 4 ml of pH 8 borate buffer in a dark, 4L polyethylene reaction vessel. This will require five 4L vessels.

(2) Measure pH and adjust, if necessary, to pH 8 with dilute H2SO4 or dilute NaOH.

(3) Dose with OP pesticide(s) to achieve a concentration of 100 µg/L or below the water solubility limit, whichever is lower.

(4) Collect the unchlorinated, pesticide spiked OP sample.

(5) Add pH 8 hypochlorite-buffer solution to give an initial free chlorine residual of 4.0 ± 0.4 mg/L Cl2 and a subsequent free chlorine residual of > 1.0 ± 0.4 mg/L at 24 hours. Dose the appropriate volume of hypochlorite-buffer solution to give the required dose in the 2L sample. The time of chlorination is T = 0.

(6) Prior to taking water samples, stir solution with the aid of magnetic stirring bar for two minutes.

(7) Take samples at the time intervals for analysis summarized in Table 2:

OP pesticide – 0 (prechlorination), 1 hr, 4 hr, 24 hr, 72 hr
Transformation products (oxon, sulfoxide, sulfone, sulfone oxon, sulfoxide oxon) – 0 (prechlorination), 1 hr, 4hr, 24 hr, 72 hr

(8) The samples are immediately withdrawn from the reaction vessel and then quenched stoichiometrically with sodium thiosulfate (with slight excess) based on the free chlorine residual [1.25 mg per 100 ml aliquot]. The samples should be stored in the dark at 0 - 4°C, if they cannot be analyzed right away.

(9) Separate samples will be taken to measure the free chlorine residual, pH, and temperature.

(10) Analyze the quenched samples for the parent compound, primary product (oxon) by appropriate analytical method (GC/MS or LC/MS/MS). Other transformation products will be identified, when possible, and described as tentatively identified compounds.

ii. For Treatment B:

(1) Put 2L of unchlorinated Fisher Environmental Grade water and add 4 ml of pH 8 borate buffer in a dark, 4L polyethylene reaction vessel.

(2) Measure pH and adjust, if necessary, to pH 8 with dilute H2SO4 or dilute NaOH.

Dose with OP pesticide(s) to achieve a concentration of 100 µg/L or below the water solubility limit, whichever is lower.

(3) At approximately the same time as the collection of the chlorinated samples in Treatment A, collect the unchlorinated, pesticide spiked OP samples at 0, 1, 4, 24 and 72 hours. The samples should be stored in the dark at 0 - 4°C, if they cannot be analyzed right away.

(4) Separate samples will be taken to measure the pH and temperature.

(5) Analyze the samples for the parent compound, primary product (oxon) by appropriate analytical method (GC/MS or LC/MS/MS). Other transformation products will be identified, when possible, and described as tentatively identified compounds.

iii. For Treatment C:

(1) Put 2L of unchlorinated Fisher Environmental Grade water and add 4 ml of pH 8 borate buffer in a dark, 5L polyethylene reaction vessel.

(2) Measure pH and adjust, if necessary, to pH 8 with dilute H_2SO_4 or dilute NaOH.

(3) Add pH 8 hypochlorite-buffer solution to give an initial free chlorine residual of 4.0 ± 0.4 mg/L Cl_2 and a subsequent free chlorine residual of > 1.0 ± 0.4 mg/L at 24 hours. Dose the appropriate volume of hypochlorite-buffer solution to give the required dose in the 2L sample.

(4) Prior to taking water samples, stir solution with the aid of magnetic stirring bar for two minutes.

(5) Collect a sample after about 1 hour for OP pesticides and for oxons.

(6) The sample is withdrawn from the reaction vessel and then quenched with the selected reducing agent (with slight excess) based on the free chlorine residual [1.25 mg per 100 ml aliquot]. The aliquots should be stored in the dark at 0 - 4° C, if they cannot be analyzed right away.

(7) A separate sample will be taken to measure the free chlorine residual, pH, and temperature at 1 hour.

(8) Analyze the sample for the parent compound, primary product (oxon) by appropriate analytical method (GC/MS or LC/MS/MS). Other transformation products will be identified, when possible, and described as tentatively identified compounds.

iv. For Treatment D:

(1) Put 2L of unchlorinated Fisher Environmental Grade water and add 4 ml of pH 8 borate buffer in a dark, 5L polyethylene reaction vessel.

(2) Measure pH and adjust, if necessary, to pH 8 with dilute H2SO4 or dilute NaOH.

(3) Collect 100 ml samples of the unchlorinated, buffered water at each sampling interval of 0, 1, 4, 24, and 72 hours.

(4) These samples will be spiked with the OP pesticide(s) and oxon(s) at a spiking level of 50 ppb, as necessary.

(6) The samples will be stored for possible analysis with sample set batches. The samples should be stored in the dark at 0-4° C, if they cannot be analyzed right away.

(7) A separate sample is taken to measure the pH and temperature.

(8) Analyze the samples for the parent compound, primary product (oxon) by appropriate analytical method (GC/MS or LC/MS/MS). Other transformation products will be identified, when possible, and described as tentatively identified compounds.

Table II.E-2.4 Proposed Sampling and Analysis Regime

Treatment Condition (Treated Water Samples and Controls: OP pesticide)	Sampling Times				
	Pre-chlorination	Postchlorination			
A1 OP Cl_2 H_2O **A2** OP Cl_2 H_2O	0	1 hr	4 hrs	24 hrs	72 hrs
	OP	OP	OP	OP	OP
	Oxon[1]	Oxon	Oxon	Oxon	Oxon
		Cl	Cl	Cl	Cl
B OP H2O	OP	OP	OP	OP	OP
	Oxon	Oxon	Oxon	Oxon	Oxon
C Cl2 H2O		OP			
		Oxon			
		Cl			
D H_2O	Spiked OP	Spiked OP	Spiked OP	Spiked OP	Spiked OP
	Spiked Oxon	Spiked Oxon	Spiked Oxon	Spiked Oxon	Spiked Oxon

1- Sulfone, sulfoxide, sulfone oxon, and sulfoxide oxon will be analyzed if appropriate for the test pesticide. This assumes analytical methods and analytical standards are available for the various degradation products.

j. Data Reduction and Reporting

Report detections of parent OP and its degradation products. Calculate concentrations, when possible, of OP pesticides and their stability products. Report identities and structural formulas of transformation products.

k. Interpretation of Results

The interpretation of study results will be dependent on the detection of oxidation products in the chlorinated test water treatments. The control treatments will be used to assess whether the OP pesticide undergoes oxidation in non-chlorinated laboratory water and to assess whether OP pesticide or its oxidation products are in the chlorinated water without pesticide dosing. Because the experimental design has minimal replication and the analytical methods are not fully vetted for all the OP pesticides and their oxidation products, there will be **strict qualitative interpretation** (i.e. presence or absence of oxidation products) on whether OP pesticides [phorate, disulfoton, and terbufos] undergo oxidative desulfonation during a 72 hour contact time in chlorinated laboratory water. This deduction will be reached if their oxidation products [sulfoxides and sulfones and their associated sulfoxide and sulfone oxons] are detected at any quantifiable level in either replication in the chlorinated laboratory water treatments at any sampling time and the OP pesticide is stable in non-chlorinated laboratory water. Additionally, the detection of oxidation products in chlorinated water at the 24 hour or 72 hour sampling times will suggest the oxidation product is stable enough in chlorinated water to have the potential for dietary exposure through drinking water

l. References

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USEPA, Laboratory Study on the Effects of Chlorinated Water on OP Pesticides, Quality Assurance Project Plan, OPP/EFED/WTEWG, April 24, 2006.

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9. Appendix 2: Results for the Laboratory Study on the Effects of Chlorinated Water on OP Pesticides, Phase II

Table II.E-2.5 Results of the LC/MS/MS Analyses of the OP Pesticides Terbufos, Phorate and Disulfoton and Degradation in Chlorinated and Unchlorinated Water

Sample	Sample Time	parent	oxon	Sulfox-ide	sulfone	oxon sulfox-ide	oxon sulfone
MDL		5	5	10	25	4	4
Terbufos							
A1	0	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.
	15 min	N.D.	N.D.	N.D.	N.D.	35	N.D.
	4 h	N.D.	N.D.	N.D.	N.D.	4	N.D.
	24 h	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.
	72 h	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.
A2	0	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.
	15 min	N.D.	N.D.	N.D.	N.D.	31	N.D.
	4 h	N.D.	N.D.	N.D.	N.D.	5	N.D.
	24 h	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.
	72 h	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.
B	0	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.
	15 min	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.
	4 h	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.
	24 h	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.
	72 h	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.
C		N.D.	N.D.	N.D.	N.D.	N.D.	N.D.
D	0	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.
	15 min	N.D.	41	37	42	52	55
	4 h	N.D.	34	32	41	49	54
	24 h	N.D.	34	33	47	50	48
	72 h	N.D.	38	34	39	51	53
Phorate							
A1	0	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.
	15 min	N.D.	N.D.	N.D.	N.D.	73	N.D.
	4 h	N.D.	N.D.	N.D.	N.D.	35	5
	24 h	N.D.	N.D.	N.D.	N.D.	N.D.	8
	72 h	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.
A2	0	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.
	15 min	N.D.	N.D.	N.D.	N.D.	82	N.D.
	4 h	N.D.	N.D.	N.D.	N.D.	47	4
	24 h	N.D.	N.D.	N.D.	N.D.	N.D.	6
	72 h	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.
B	0	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.
	15 min	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.
	4 h	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.

Sample	Sample Time	parent	oxon	Sulfox-ide	sulfone	oxon sulfox-ide	oxon sulfone
MDL		5	5	10	25	4	4
	24 h	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.
	72 h	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.
C		N.D.	N.D.	N.D.	N.D.	N.D.	N.D.
D	0	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.
	15 min	N.D.	45	69	33	49	50
	4 h	N.D.	41	56	35	44	42
	24 h	N.D.	42	56	37	49	45
	72 h	N.D.	47	83	39	53	47
Disulfoton							
A1	0	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.
	15 min	N.D.	N.D.	N.D.	N.D.	54	21
	4 h	N.D.	N.D.	N.D.	N.D.	N.D.	54
	24 h	N.D.	N.D.	N.D.	N.D.	N.D.	47
	72 h	N.D.	N.D.	N.D.	N.D.	N.D.	26
A2	0	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.
	15 min	N.D.	N.D.	N.D.	N.D.	51	24
	4 h	N.D.	N.D.	N.D.	N.D.	N.D.	54
	24 h	N.D.	N.D.	N.D.	N.D.	N.D.	41
	72 h	N.D.	N.D.	N.D.	N.D.	N.D.	23
B	0	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.
	15 min	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.
	4 h	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.
	24 h	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.
	72 h	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.
C		N.D.	N.D.	N.D.	N.D.	N.D.	N.D.
D	0	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.
	15 min	N.D.	42	40	42	51	65
	4 h	N.D.	40	45	41	54	54
	24 h	N.D.	40	37	39	49	50
	72 h	N.D.	38	40	40	53	55

Table II.E-2.6 Results of the ECB GC-MSD Analyses of the OP Pesticides Terbufos, Phorate and Disulfoton and Degradation in Chlorinated and Unchlorinated Water

Sample	Sample Time	parent	oxon	Sulfox-ide	sulfone	oxon sulfox-ide	oxon sulfone
Terbufos							
MDL		**1**	**3**		**1**		**1**
A1	**0**	51	N.D.		N.D.		N.D.
	15 min	N.D.	N.D.		N.D.		N.D.
	4 h	N.D.	N.D.		N.D.		N.D.
	24 h	N.D.	N.D.		N.D.		N.D.
	72 h	N.D.	N.D.		N.D.		N.D.
A2	**0**	59	N.D.		N.D.		N.D.
	15 min	N.D.	N.D.		N.D.		N.D.
	4 h	N.D.	N.D.		N.D.		N.D.
	24 h	N.D.	N.D.		N.D.		N.D.
	72 h	N.D.	N.D.		N.D.		N.D.
B	**0**	N.A.	N.A.		N.A.		N.A.
	15 min	73	N.D.		N.D.		N.D.
	4 h	23	N.D.		N.D.		N.D.
	24 h	7	N.D.		N.D.		N.D.
	72 h	2	N.D.		N.D.		N.D.
C		N.D.	N.D.		N.D.		N.D.
D	**0**	N.A.	N.A.		N.A.		N.A.
	15 min	N.A.	N.A.		N.A.		N.A.
	4 h	29	36		47		52
	24 h	44	52		56		59
	72 h	33	35		48		42
Phorate							
MDL		**1**	**3**		**1**		**2**
A1	**0**	56	N.D.		N.D.		N.D.
	15 min	N.D.	N.D.		N.D.		N.D.
	4 h	N.D.	N.D.		N.D.		4
	24 h	N.D.	N.D.		N.D.		2
	72 h	N.D.	N.D.		N.D.		N.D.
A2	**0**	63	N.D.		N.D.		N.D.
	15 min	N.D.	N.D.		N.D.		N.D.
	4 h	N.D.	N.D.		N.D.		4
	24 h	N.D.	N.D.		N.D.		2
	72 h	N.D.	N.D.		N.D.		N.D.
B	**0**	N.A.	N.A.		N.A.		N.A.
	15 min	78	N.D.		N.D.		N.D.
	4 h	29	N.D.		N.D.		N.D.
	24 h	14	N.D.		N.D.		N.D.
	72 h	8	N.D.		N.D.		N.D.
C		N.D.	N.D.		N.D.		N.D.

Sample	Sample Time	parent	oxon	Sulfox-ide	sulfone	oxon sulfox-ide	oxon sulfone
D	0	N.A.	N.A.		N.A.		N.A.
	15 min	N.A.	N.A.		N.A.		N.A.
	4 h	27	31		47		46
	24 h	43	48		57		50
	72 h	35	32		49		42
Disulfoton							
MDL		1	1	1	3	3	3
A1	0	58	N.D.	3	N.D.	5	N.D.
	15 min	N.D.	N.D.	N.D.	N.D.	N.D.	36
	4 h	N.D.	N.D.	N.D.	N.D.	N.D.	38
	24 h	N.D.	N.D.	N.D.	N.D.	N.D.	22
	72 h	N.D.	N.D.	N.D.	N.D.	N.D.	14
A2	0	66	N.D.	4	N.D.	3	N.D.
	15 min	N.D.	N.D.	N.D.	N.D.	15	36
	4 h	N.D.	N.D.	N.D.	N.D.	N.D.	29
	24 h	N.D.	N.D.	N.D.	N.D.	N.D.	20
	72 h	N.D.	N.D.	N.D.	N.D.	N.D.	17
B	0	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.
	15 min	77	N.D.	3	N.D.	4	N.D.
	4 h	33	N.D.	3	N.D.	N.D.	N.D.
	24 h	2	N.D.	2	N.D.	N.D.	N.D.
	72 h	3	N.D.	3	N.D.	N.D.	N.D.
C		N.D.	N.D.	N.D.	N.D.	N.D.	N.D.
D	0	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.
	15 min	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.
	4 h	31	31	43	47	28	58
	24 h	44	44	46	52	25	60
	72 h	36	35	46	35	23	49

E-3. Water Outputs – Region A

See file Water Outputs – Region A.xls

E-4. Water Outputs – Region B

See file Water Outputs – Region B.xls

E-5. Water Outputs – Region C

See file Water Outputs – Region C.xls

E-6. Water Outputs – Region D

See file Water Outputs – Region D.xls

E-7. Water Outputs – Region E

See file Water Outputs – Region E.xls

E-8. Water Outputs – Region F

See file Water Outputs – Region F.xls

E-9. Water Outputs – Region G

See file Water Outputs – Region G.xls

G-1. Sensitivity Analysis: Cancellation of Azinphos-Methyl Group 3 Uses

A. Background

The food component of the Organophosphorus Cumulative Risk Assessment (OP CRA) is to a large extent based on pesticide residue information collected by USDA's Pesticide Data Program (PDP) from 1994 to 2004. The PDP sampling design and procedures provide OPP with a nationally representative sample of selected food commodities available to the US population in grocery stores.

Inherent in the use of such monitoring data that has been collected over an extended length of time is the concern that any changes in pesticide use patterns will not be reflected in the data. The OPs in particular have undergone sizable changes in use patterns as a result of the individual chemical decisions. In cases for which legal agreements have been signed or voluntary cancellations implemented, the uses have been removed from the assessment.

The OP CRA Update 2006 has incorporated the phase-out of domestic uses that was recently proposed by the Agency concerning the remaining (Group 3) uses of azinphos-methyl (AZM). Specifically, all domestic uses for AZM on almonds, Brussels sprouts, pistachios, walnuts, apples, blueberries, cherries, parsley, and pears are to be phased out effective in 2007 or 2010. This information was incorporated into this Update by removing from the food assessment all AZM residues on these crops which are domestically-grown[25]; residues on imported crops were not changed. All other uses of this pesticide have already been voluntarily cancelled by the manufacturer.

These mitigation actions for AZM were proposed due primarily to issues associated with worker exposure, and not dietary exposure. Thus, dietary risk and exposure estimates presented in OP CRA Update 2006 are not expected to differ significantly from those that do not incorporate these 2007 and 2010 AZM proposed use cancellations.

The purpose of this sensitivity analysis is to determine the extent to which the inclusion of domestic AZM residues on Group 3 crops affect the exposure and risk estimates presented in Chapter I.C.

[25]As part of its standard sampling procedure, USDA PDP collects detailed information for each of the hundreds of samples collected each year. An essential component of this detailed sampling information is the origin of sample. Specifically whether the food commodity was grown domestically or imported.

B. Approach

In the food component of the OP CRA Update 2006, PDP analytical samples of AZM residues identified as domestic in origin were completely removed from the assessment. As a sensitivity analysis and to ensure that risks prior to any use cancellations are not above the Agency's level of concern, OPP has performed a parallel exposure analysis in which AZM Group 3 domestic uses are retained.

PDP samples of domestic origin that were analyzed for residues of AZM (or its metabolite) were included in this sensitivity analyses for any commodities that are used by OPP to represent pesticide residues in almonds, Brussels sprouts, pistachios, walnuts, apples, blueberries, cherries, parsley, and pears[26]. All other residue and consumption information from the food component of the OP CRA Updated 2006 remained unchanged for this sensitivity analysis (see Chapter I.C for details). Resulting exposure and risk estimates under this scenario would be expected to be more typical of the near term (e.g., through 2007 and 2010) before the AZM Group 3 cancellation becomes effective.

C. Results

In Chapter I.C, the margins of exposure (MOEs) at 95th, 99th, and 99.9th percentiles of exposure are reported for the 21-day exposure period for various age groups, the mostly highly exposed of which were children 1-2 and 3-5 years old. Briefly, the MOEs for the 21-day assessment are above or very close to the target of 100 at the 99.9th percentile of exposure for all age groups; the MOEs for the 95th and 99th percentiles of exposure are well above 100.

Table II.G-4.1 provides a comparison of MOEs at 99.9th percentiles of exposure from the 21-day food assessment presented in Chapter I.C and the 21-day food assessment described in this Appendix. Tables II.G-4.2 and II.G-4.3 provide similar comparisons of the MOEs at the 99th and 95th percentiles of exposure. Although only two most highly exposed age groups are presented in these Tables, the MOEs for the all other age groups exceed the target MOE of 100 at the percentiles presented.

[26] For detailed information regarding crops and foods to which PDP commodities are translated see Appendices II.C.4 and II.C.6.

Table II.G-1.1 Cumulative Food Assessment MOEs at the 99.9th Percentile Exposure.

	Single Day MOE without AZM Group 3 Uses	Single Day MOE with AZM Group 3 Uses
Children 1-2 yrs	110	110
Children 3-5 yrs	99	98

Table II.G-1.2 Cumulative Food Assessment MOEs at the 99th Percentile.

	Single Day MOE without AZM Group 3 Uses	Single Day MOE with AZM Group 3 Uses
Children 1-2 yrs	250	240
Children 3-5 yrs	300	290

Table II.G-1.3 Cumulative Food Assessment MOEs at the 95th Percentile of Exposure.

	Single Day MOE without AZM Group 3 Uses	Single Day MOE with AZM Group 3 Uses
Children 1-2 yrs	550	520
Children 3-5 yrs	670	620

D. Conclusions

When these Group 3 AZM uses are included in this alternative assessment (i.e, incorporated back into the exposure and risk calculations), MOEs at the 99.9th percentile of exposure remain virtually unchanged for children 1-2 and change from 99 to 98 for children 3-5. Thus, the AZM use cancellations that have been proposed to take effect in 2007 to 2010 do not significantly impact the dietary exposure and risk estimates presented in the OP CRA Update 2006.

G- 2. Characterization of Potential Oxon Formation and Exposure in Drinking Water

A number of OP pesticides have the potential to convert to more toxic oxon transformation products as a result of chlorination/oxidation during standard drinking water treatment. Additional studies conducted since 2002 confirm the potential for OP pesticides to form stable oxon transformation products as a result of chlorination. Less data are available characterizing the potency of most oxons For those oxons with insufficient toxicity information, EPA used high end adjustment factors of 10X and 100X to account for the potential increased potency of the oxon relative to the parent. With protective assumptions (100% conversion from the parent to the oxon, instantaneous transformation to oxon with no degradation), EPA estimated that the oxons would not appreciably change the cumulative OP distributions with a 10X or, in most scenarios, with the 100X oxon adjustment factor. As described in detail below, the exception is for Region C (Southwest / Central Valley, CA, exposure scenario) where the 100X oxon adjustment factor increased estimated peak cumulative concentrations by as much as 35-50X, largely due to methidathion. Overall, EPA's continues to conclude that risk from drinking water exposure to OPs is below the level of concern for the cumulative risk assessment. As described below, the increase in peak cumulative concentrations for methidathion are believed to result from compounding high end assumptions on the potency and the exposure to the oxon. This compounding decreases the confidence surrounding the risk estimates.

This appendix characterizes the degree of confidence and uncertainty in regarding oxon formation and decline and oxon toxicity and identifies additional information needed to quantify the potential impacts of oxon formation on the OP cumulative exposure in drinking water.

1. Screening Level Approach: Potential for Oxon Formation as a Result of Drinking Water Treatment

For the OP pesticides, information on the potential to form oxons as a result of chlorination and on differential toxicities between parent and oxon are not sufficient to make quantitative adjustments to the cumulative exposure estimates. The Agency has used a screening level approach to evaluate the potential contribution of potential oxon exposure in drinking water to the cumulative risk of the OPs. The purpose of this analysis was

1) to consider the degree to which exposure to the oxons from drinking water may qualitatively change the Agency's conclusion that the risk from drinking water

exposure to OPs is below the level of concern and

2) to determine whether additional information may be needed concerning oxon toxicity, extent and rate of oxon formation as a result of standard drinking water treatment, and/or the rate of breakdown of the oxons after formation in order to better refine and quantify risk to the oxons.

Based on published literature, registrant-submitted studies, US EPA laboratory studies (summarized in Appendices II.E.1 and II.E.2), and monitoring data (most notably a 1999-2000 USGS reservoir monitoring study; see Bloomquist et al, 2001), EPA has identified ten OP pesticides with the potential to form stable oxons as a result of chlorination: azinphos methyl, bensulide, chlorethoxyphos, chlorpyrifos, diazinon, dimethoate, disulfoton sulfone, malathion, methidathion, methyl parathion, and phostebuipirim. The supporting evidence is summarized in Table I.E-2 of the drinking water exposure section (I.E) and in Appendices II.E-1 and II.E.2. The studies summarized in Table I.E-2 are only designed to determine whether oxons form as a result of chlorination and whether they are stable for at least 72 hours after formation. More extensive studies would be required to determine the rates of formation and decline of oxons in treated water.

2. Estimating the Impacts of Potential Oxon Formation on OP Cumulative Distributions in Drinking Water

In estimating potential oxon impacts, the Agency assumed that any transformation as a result of chlorination results in complete conversion to the oxon and that the resulting oxon would be stable for at least 72 hours, sufficient time to move through the distribution system. The resulting estimates of oxon residues in drinking water represent an upper bound of the potential oxon levels that may actually occur in drinking water. As mentioned earlier, the studies referenced in Table I.E-2 were not designed to determine definitively what percentage of the parent OP might convert to the oxon. While this percentage is likely to vary depending on treatment conditions, anything less than 100% conversion will result in lower oxon levels than estimated. Similarly, the Agency's assumption that the oxons remain stable after they are formed is an upper bound estimate of the extent that the oxons degrade at any appreciable rate between the time they are formed to when they are distributed at the tap.

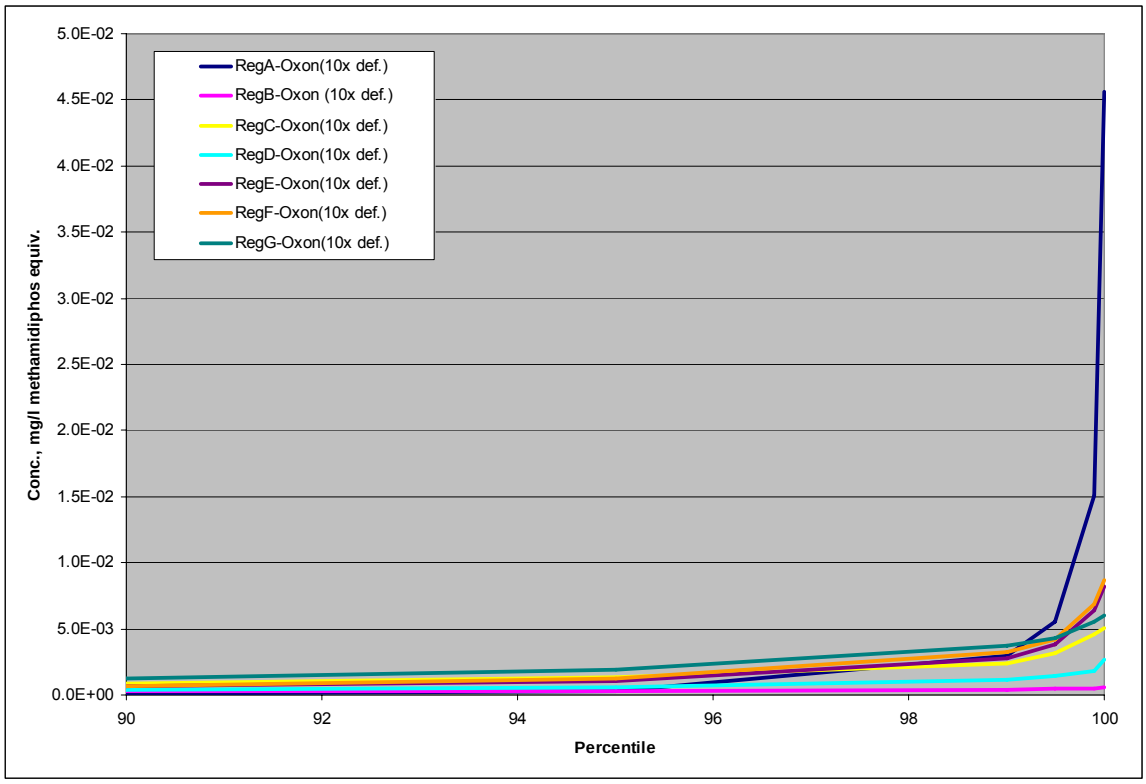
EPA had sufficient data to estimate oxon adjustment factors that reflect the greater toxicity of the oxon for three OP pesticides - dimethoate (3X), chlorpyrifos (10X) and methyl parathion (10X). For the remaining OP pesticides which form oxons, insufficient data exists to determine a potential oxon adjustment factor. For these pesticides, the Agency used

oxon adjustment factors of 10X and 100X to consider upper bound estimates of potential oxon potentcy. These adjustment factors were applied to the pesticide concentrations in water.

As noted in the drinking water exposure section (I.E), the exposure scenario for Region A (Florida) had the highest estimated peak concentrations of any of the regional scenarios. Because none of the OP residues driving exposure in this region formed oxons, this regional distribution served as a reference point to compare the impact of oxon formation on drinking water exposures in other regions.

While the 10X oxon adjustment factor resulted in increases in estimated peak concentrations ranging from less than 25% to 3-5X (Region C), **all** of the regional distributions remained well below that of Region A (Figure II.G.2 1) and thus below the level of concern for the cumulative risk assessment. Peak concentrations from the Region A scenario (dark blue line in the figure) is at least 6X to more than an order of magnitude greater than those from any other region.

Figure II.G-2.1 Frequency distribution of each of the regional OP cumulative drinking water exposures, including oxon adjustment factors (10X).



When the 100X oxon adjustment factor is applied, peak concentrations in Regions B, C, E, F, and G shifted upwards in relation to that of Region A but remained below the below the level of concern for the

cumulative risk assessment. The noted exception is for the cumulative distribution for Region C which increased by 30 to 50X, surpassing the distribution of Region A (Figure II.G.2 2), primarily due to the oxon of methidathion. This resulted in estimated MOEs for drinking water exposure ranging from 16 to 99 for the first third of the year for children 1 to 2 years of age at the 99.9th percentile (21-day rolling average) (Figure II.G.2 3).

Figure II.G-2.2 Frequency distribution of each of the regional OP cumulative drinking water exposures, including oxon adjustment factors (100X).

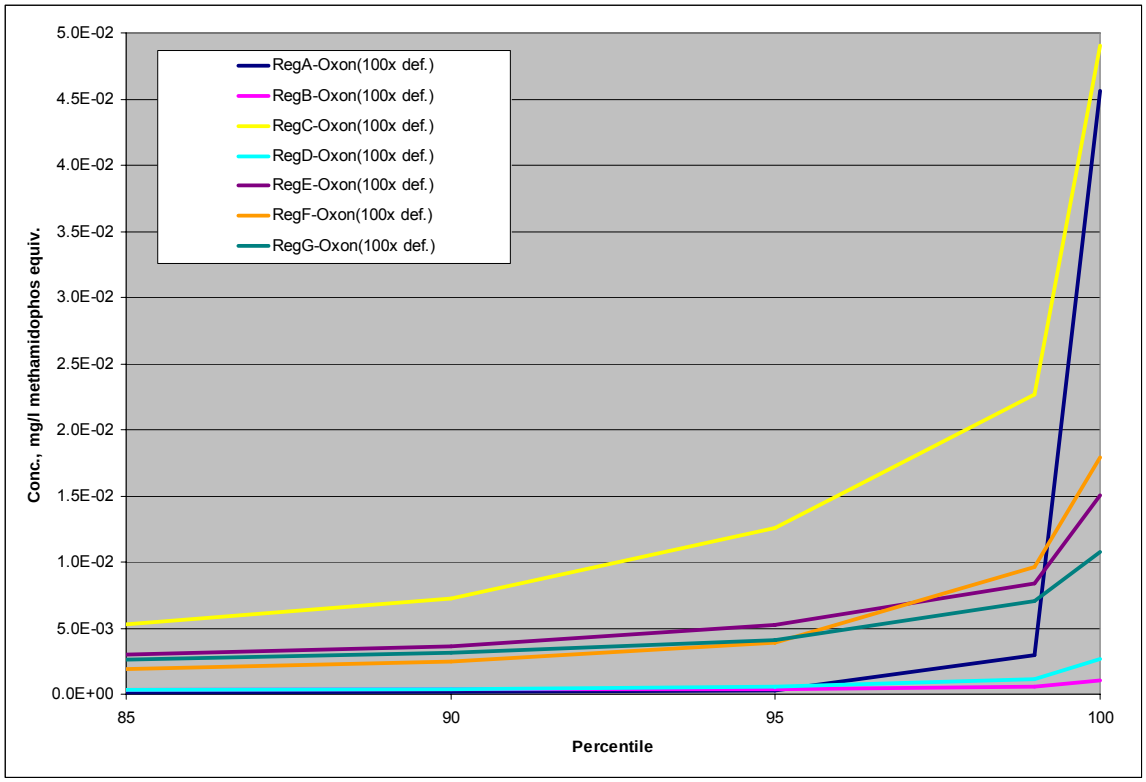
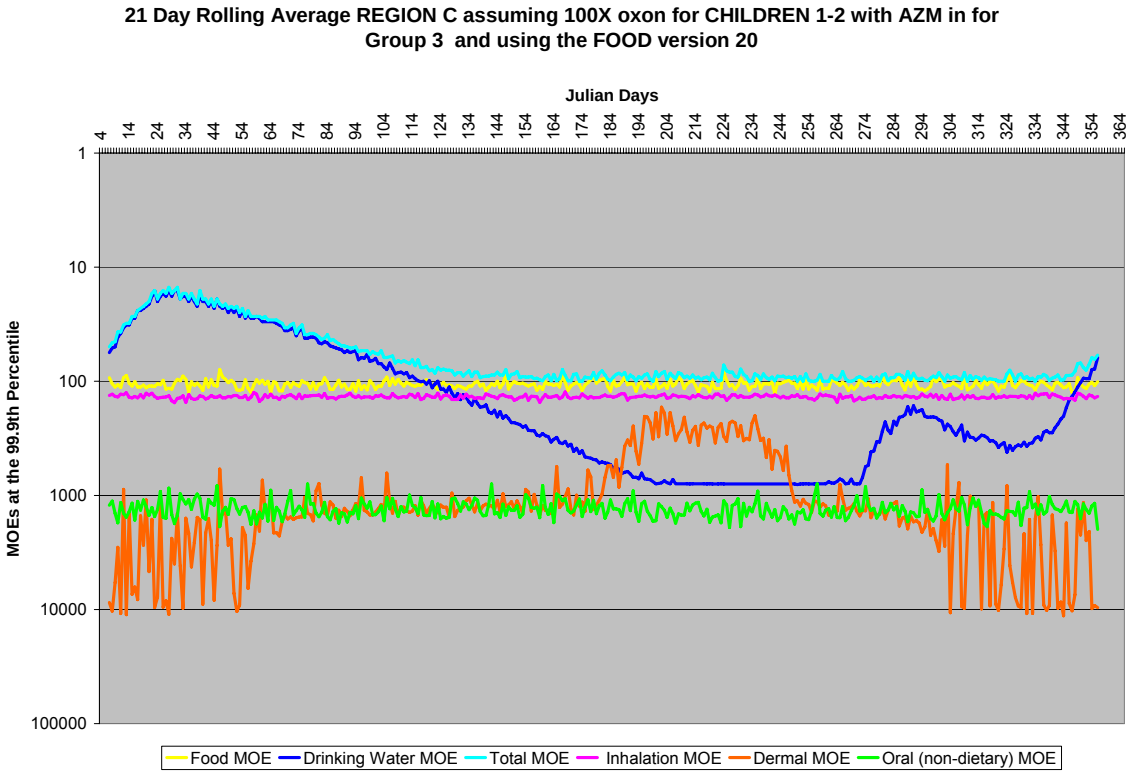


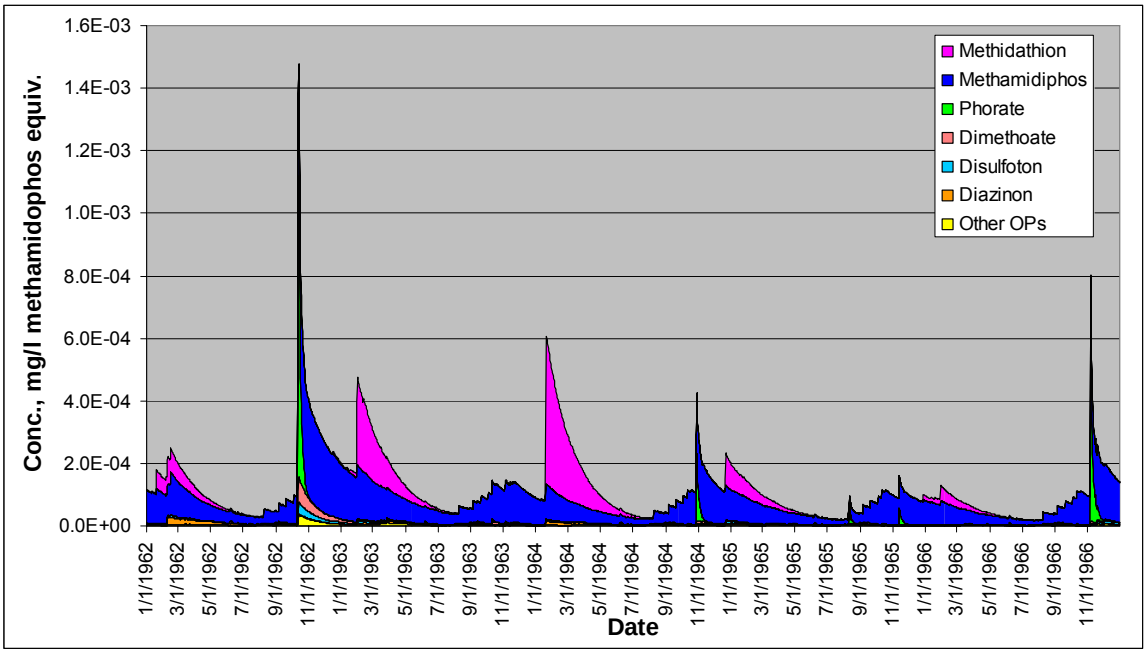
Figure II.G-2.3 Margins of Exposure (MOE) for Cumulative OP Residues from Multiple Routes of Exposure in Region C for Children 1-2 Years Old at the 99.9th Percentile of Exposure.



3. Characterizing Oxon Exposure in Region C

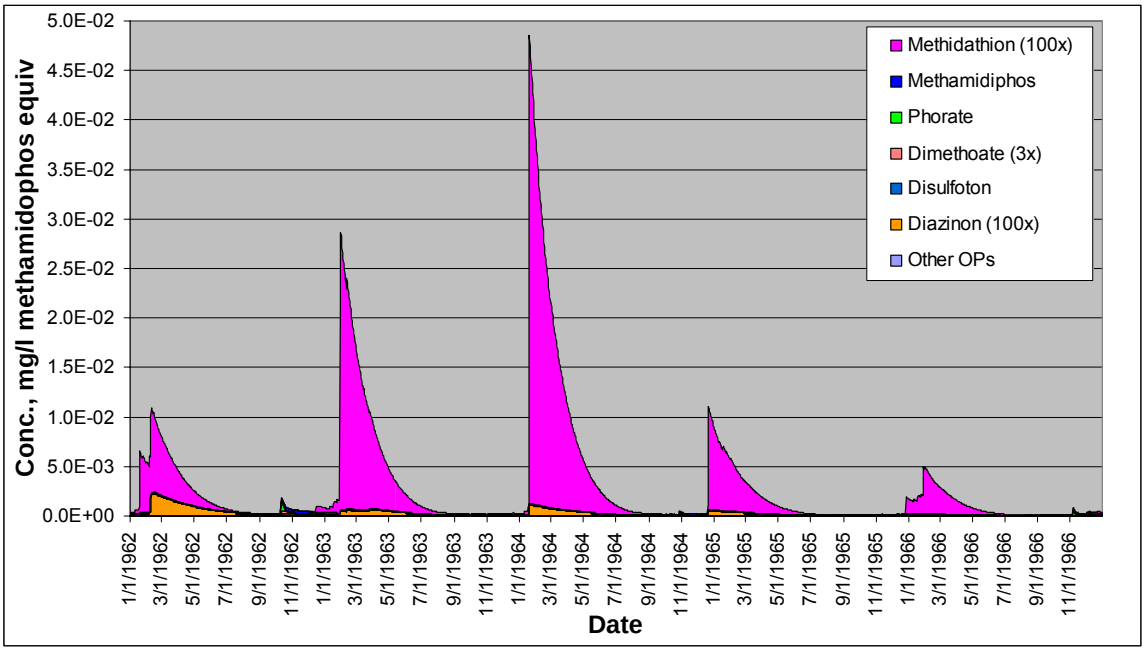
The exposure scenario for Region C includes a number of oxon formers with peak concentrations within two orders of magnitude of the cumulative peaks (chlorpyrifos, diazinon, dimethoate, methidathion, methyl parathion). With no oxon adjustments taken into account, the major OP pesticides contributing to the cumulative OP residues are methamidiphos, methidathion, and phorate (including the sulfone and sulfoxide residues). Figure II.G.2 4 provides a representative illustration of the relative contributions of OP residues to the cumulative exposure across 4 years (of a 35-year simulation). Of the major contributors, only methidathion has the potential to form an oxon as a result of chlorination.

Figure II.G-2.4 Contributions of individual OP pesticides to the RPF-adjusted cumulative load for Region C (CA Central Valley) with no oxon adjustment factor.



When the100X oxon adjustment factor is used, methidathion becomes the dominant contributor to the OP cumulative exposure (Figure II.G.2 5). Note that the scale of the graph increases by 30X between the two figures. The phorate peak shown in 1962 (Figure II.G.2 4), which remains unchanged because no oxons are formed, is dwarfed in Figure II.G.2 5 while the methidathion peaks increase with the oxon adjustment factor.

Figure II.G-2.5 Contributions of individual OP pesticides to the RPF-adjusted cumulative load for Region C (CA Central Valley) with a default 100X oxon adjustment factor.



4. Characterizing the Risk to Methidathion Oxon

The Agency has taken a screening approach to evaluating the impact of direct exposure to oxons derived from drinking water processing chlorination. This approach included high end assumptions for conversion from the parent to the oxon, stability of the oxon, and the toxicity of oxon degradate. These assumptions used in combination result in exaggerated risk to the oxon. Even with these high end assumptions, the risk from the oxons are below the level for the majority of scenarios, including all scenarios which used the 10X toxicity adjustment factor. The noted exception was for methidathion oxon in Region C when using the 100X toxicity adjustment factor.

Methidathion was included in the 2006 USEPA BEAD study (Appendix II.E.1). Although the studies were not designed to make quantitative estimates of oxon formation and decline, it does provide an indication of the relative degree of oxon formation and stability. Methidathion was stable in buffered, nonchlorinated water. In other word, there is potential for it to persist in the water as it goes through the treatment plant. Methidathion converted fairly rapidly under chlorination - 90-98% conversion to the oxon within 1 hr. These data suggest that the assumption that 100% of the parent compound converts to the oxon is not unreasonable. After 72 hr, two-thirds of the oxon was still detected,

suggesting that methidation-oxon is fairly stable within the perspective of a DW treatment distribution system.

Monitoring data on methidathion is scarce, particularly in methidathion use areas. While methidathian was not included in the USGS NAWQA study, a study conducted by California DPR and USGS found methidathion detections from dormant spray to orchards in 18% of water samples monitored (see Water Appendix III.E 2 from the 2002 OP CRA). The modeled exposure for methidation has a maximum of 0.15 ppb and a 99th percentile concentration of 0.06 ppb. These concentrations are comparable to maximum reported detections from available monitoring studies. Information from the USEPA BEAD study combined with the monitoring studies suggests that actual estimates of DW exposure for methidathion and its oxon are reasonable approximations of the potential concentrations in Region C where methidathion is used on orchard crops.

The relative potency of methidathion oxon compared to the parent compound for brain ChE inhibition s unknown but is expected to be lower than the 100X toxicity adjustment factor. For dimethoate, methyl parathion, and chlorpyrifos where there is sufficient information to evaluate relative potency for brain ChE inhibition, the oxon is less than 10X more potent compared to the parent for brain ChE inhibition. Theorectically, if the oxon were up to 100X more potent than the parent, then the oxon would be almost 20X more potent than dicrotophos which is the most potent OP pesticide and which does not require activation to the oxon but instead is active as the parent compound. Although not impossible, it is unlikely that methidathion oxon is actually 100X more potent that the parent. Moreover, there are no available data comparing the relative sensitivity of juvenile and adult animals (ie, a comparative ChE study) for methidathion. As such, the full 10X FQPA factor has been retained for methidathion. Overall, the Agency believes that the uncertainties associated with the toxicity of the oxon are key in the characterization of the risk to methidathion oxon in drinking water. The Agency also believes that risks reported here are exaggerated and the actual risk is significantly lower. To confim this, the Agency will be issuing a data call-in notice for a 28-day repeated-dose toxicity study with methidathion oxon.

G-3. Characterization of OP Cumulative Residues in Drinking Water: Region A

EPA estimated distributions of individual and cumulative OP pesticide residues in drinking water in high potential exposure areas across different regions of the country. In the south Florida scenario, which represents the few surface water sources of drinking water in Region A, estimated concentrations of total phorate residues (parent plus sulfoxide and sulfone transformation products) reached as high as 1 to 11 ug/l (ppb) for periods of short duration (days). The transformation products form in the environment and, based on available literature, are expected to be equal in toxicity to phorate. These phorate peaks drove the OP cumulative exposure estimates for drinking water in this region, resulting in MOEs ranging from 79 to 94 for Children 1-2 year old at the 99.9th percentile of exposure on days 229 to 244.

The drinking water exposure estimated for this region is likely an overestimate because laboratory studies indicate that phorate and its sulfoxide and sulfone transformation products are likely to break down rapidly (on the order of minutes to hours) during the chlorination process of drinking water treatment (see Appendices II.E.1 and II.E.2) In addition, the estimated concentrations of total phorate residues are likely to be overestimates for the following reasons:

- Peak concentrations assume that phorate applications on sugarcane occur on the same day. Because of the estimated acreage being treated, phorate applications are likely to be spread out over time. Thus, the peak concentrations are likely to be lower than estimated.

- The estimated phorate concentrations better reflect concentrations in drainage canals and water retention structures. Reductions in concentrations are likely to occur with holding time (phorate residues degrade with half-lives on the order of days in aquatic environments) and with dilution as the drainage waters flow into larger water bodies used for drinking water supplies.

While these factors cannot be quantified, qualitatively they indicate that concentrations of total phorate residues in drinking water will be substantially lower than estimated for this region. This appendix characterizes the estimated total phorate concentrations for those high-exposure drinking water sources in south Florida and documents the lines of evidence indicating that actual OP levels in drinking water will be lower than estimated.

1. Estimated Exposures for Drinking Water in Region A

Of the OP pesticides used in the south Florida region, phorate had the highest estimated concentrations (Table II.G.3 2). The phorate residues in Table II.G.3 1 reflect a combination of the parent phorate and the sulfoxide and sulfone transformation products.

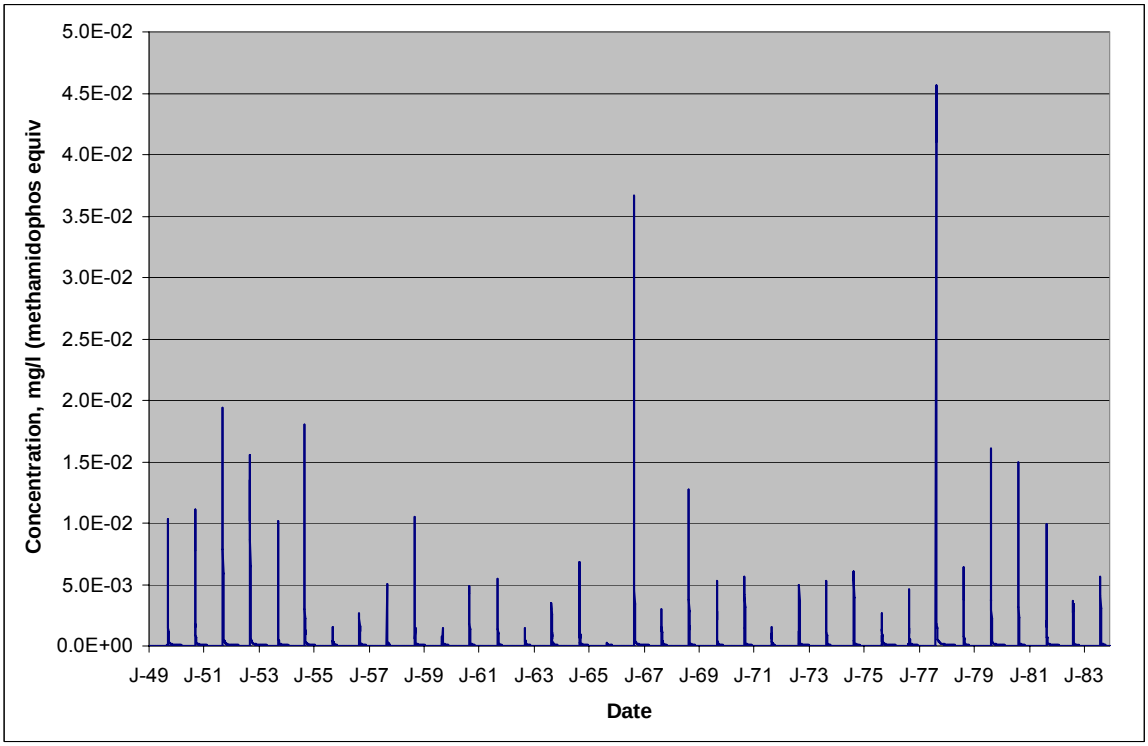
Table II.G-3.1 Estimated percentile concentrations of individual OP pesticides in the south Florida surface water exposure scenarios (not adjusted for relative potency).

Chemical	Crop/Use	Percentile concentration in ug/l (ppb)				
		Max	99th	95th	90th	80th
Region A (Florida): South FL						
Acephate	Peppers	7.6E-02	6.8E-03	8.5E-04	2.8E-04	8.7E-05
Chlorpyrifos	Corn, citrus	2.0E-01	9.6E-02	4.9E-02	3.3E-02	2.1E-02
Diazinon	Lettuce, tomato	2.9E-02	1.5E-02	8.8E-03	6.1E-03	3.9E-03
Ethoprop	Sugarcane	1.5E+00	5.1E-01	2.5E-01	1.7E-01	9.8E-02
Methamid-ophos	Acephate degradate, tomato	9.3E-03	1.7E-03	2.6E-04	8.4E-05	1.6E-05
Phorate (1)	Corn, sugarcane	1.1E+01	7.2E-01	1.8E-02	1.1E-04	5.4E-09

(1) Estimated concentrations for phorate reflect combined residues of the parent and its sulfoxide and sulfone transformation products.

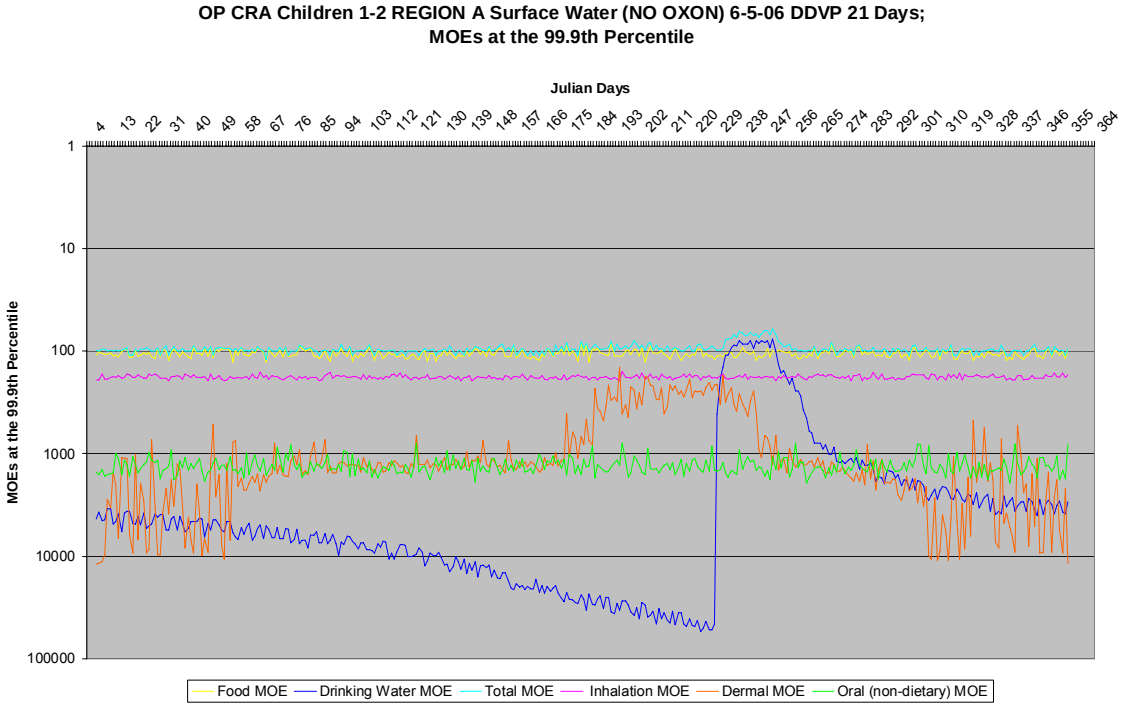
The temporal and spatial extent of potential high OP exposure is limited to a relatively short duration in the fall, associated with phorate and ethoprop applications to sugarcane. Figure II.G.3 1 shows the distribution of combined OP concentrations (in methamidophos equivalents) over 35 years of simulated weather patterns. Generally one to two brief peaks (few days in duration) occur within a short time span every year. The magnitude of the peaks varies, depending on the timing of the runoff events after application and on the magnitude of runoff. The estimated peaks assume that the applications occur on the same day every year. Year-to-year peaks are likely to vary in timing because the actual dates of application may vary within an optimal window of application from year to year. Thus, the spread in yearly peaks may be broader than shown in the figure.

Figure II.G-3.1 Estimated OP Cumulative Concentrations (in Methamidophos Equivalents) Reflecting 35 Years of Weather Data.



When the drinking water exposure estimates are folded into the cumulative exposure assessment, the estimated peak concentrations for drinking water result in MOEs ranging from 79 to 94 for children from 1-2 years in age at the 99.9th percentile (Figure II.G-3.2). The brief period of high exposure (days 229 through 244) coincide with the expected period of peak exposure based on an early September application of phorate on sugarcane and sweet corn and of ethoprop on sugarcane.

Figure II.G-3.2 Margins of Exposure (MOE) for Cumulative OP Residues Region A (Florida) for Children 1-2 Years Old at the 99.9th Percentile of Exposure.



2. Principal Contributors to the OP Cumulative Drinking Water Exposure in Region A

A CEC analysis of the 99.8th to 100th percentile of exposure to children (age 1-2 years) shows that the contributing drinking water exposures at this high end of exposure predominantly come from two drinking water years – 1977 (50% of exposures) and 1966 (20% of exposures) (Table II.G-3.2). This coincides with the two highest peak concentrations estimated for the region (Figure II.G.3 1). The estimated exposures do not represent historic exposure levels, but only the probability of exposure based on variability in weather patterns. However, the analysis indicates that the highest drinking water exposures are not driven solely by the highest water concentrations in those exposure years (Table II.G-3.2).

Table II.G-3.2 Exposure analysis for Children 1-2 Years Old For Region A (1).

Demographics						Exposure (mg/ kg-Body Wt /da)			Water	
PID-HH#	Indiv	Itera-tion	Sex	Age	Body wt (kg)	Total	Dietary	Water	Conc. (mg/l)	Year
10154 49603	2	7	F	1Y	10.5	0.0011957	0.0000062	0.0011894	0.0125	1977
20523 52340	2	6	F	2Y	13.2	0.0023352	0.0000447	0.0022905	0.0302	1977
9745 42121	3	8	M	2Y	15.9	0.0013612	0.0012711	0.0000900	0.00143	1979
20068 47302	1	8	F	1Y	10.0	0.0014643	0.0000159	0.0014484	0.0145	1966
8842 28601	1	5	F	1Y	9.5	0.0010625	0.0001106	0.0009519	0.00904	1966
19253 34813	1	1	M	2Y	11.8	0.0010390	0.0006013	0.0004376	0.00516	1979
8162 25601	3	1	F	1Y	12.3	0.0017498	0.0017483	0.0000015	1.84E-05	1965
18787 28857	1	4	F	2Y	12.3	0.0010176	0.0000572	0.0009603	0.0118	1977
6334 16123	1	3	M	1Y	10.9	0.0010806	0.0001243	0.0009563	0.0104	1977
18015 24339	1	2	M	1Y	13.6	0.0012331	0.0010390	0.0001940	0.00264	1952
6212 15150	1	4	F	1Y	15.0	0.0013518	0.0001001	0.0012517	0.0188	1977
16390 16808	1	6	M	1Y	11.4	0.0017784	0.0000445	0.0017339	0.0198	1977
5230 52024	1	3	F	2Y	13.6	0.0014841	0.0000356	0.0014485	0.0197	1977
14272 35208	1	6	M	2Y	9.5	0.0017544	0.0002197	0.0015347	0.0146	1977
5209 52015	2	8	F	1Y	9.5	0.0011210	0.0001125	0.0010085	0.00958	1977
13763 28721	2	9	M	2Y	10.0	0.0009571	0.0001491	0.0008079	0.00808	1977
4933 48010	2	6	F	1Y	11.4	0.0016704	0.0000564	0.0016140	0.0184	1966
12492 21720	1	10	M	1Y	12.3	0.0009911	0.0001691	0.0008221	0.0101	1966
4878 46511	1	2	F	2Y	13.2	0.0011330	0.0001690	0.0009640	0.0127	1977
11652 17244	1	8	F	1Y	14.5	0.0016687	0.0014836	0.0001851	0.00268	1951
4619 42505	3	3	M	2Y	12.7	0.0013135	0.0012202	0.0000933	0.00118	1952
10231 51115	8	6	F	2Y	13.6	0.0013701	0.0000125	0.0013576	0.0185	1977
3607 28010	3	1	M	1Y	10.0	0.0010041	0.0000574	0.0009468	0.00947	1966

Demographics						Exposure (mg/ kg-Body Wt /da)			Water	
PID-HH#	Indiv	Itera-tion	Sex	Age	Body wt (kg)	Total	Dietary	Water	Conc. (mg/l)	Year
19271 35305	1	6	F	1Y	9.5	0.0016609	0.0000355	0.0016254	0.0154	1977
3401 27034	3	5	M	2Y	10.9	0.0012668	0.0010322	0.0002346	0.00256	1952
18015 24339	1	4	M	1Y	13.6	0.0011644	0.0011456	0.0000187	0.000254	1959
2280 21515	1	8	F	1Y	9.5	0.0009687	0.0001143	0.0008545	0.00812	1977
14272 35208	1	7	M	2Y	9.5	0.0012525	0.0010988	0.0001537	0.00146	1969
1361 17013	5	4	M	2Y	20.5	0.0010669	0.0000757	0.0009911	0.0203	1977
12629 22731	1	5	M	1Y	11.4	0.0010534	0.0003172	0.0007362	0.00839	1966
1215 16502	1	3	F	1Y	11.4	0.0010485	0.0000754	0.0009732	0.0111	1966
11552 16751	3	6	M	2Y	15.9	0.0016186	0.0000886	0.0015300	0.0243	1977
1148 16008	1	4	M	2Y	12.3	0.0009942	0.0009483	0.0000460	0.000566	1955
19098 31824	2	3	F	1Y	10.9	0.0011833	0.0000285	0.0011548	0.0126	1977
1148 16008	1	1	M	2Y	12.3	0.0016165	0.0004836	0.0011328	0.0139	1966
14131 32216	2	5	F	2Y	12.7	0.0009783	0.0003152	0.0006631	0.00842	1977
1110 15546	3	9	F	1Y	10.5	0.0010144	0.0000318	0.0009826	0.0103	1977
20108 47804	1	10	F	1Y	15.9	0.0011481	0.0011221	0.0000260	0.000413	1953
753 14009	2	6	F	2Y	11.4	0.0013223	0.0001919	0.0011304	0.0129	1966
12467 21706	1	8	M	2Y	16.8	0.0009591	0.0000395	0.0009196	0.0154	1977
16398 16813	2	2	F	1Y	10.9	0.0013047	0.0012731	0.0000316	0.000344	1983
101 10512	1	3	F	1Y	10.0	0.0014294	0.0000200	0.0014093	0.0141	1977

(1) CALENDEX-FCID CEC Records File for CHILDREN 1-2 WATER CONSUMPTION35
CSFII 1994-98

Analysis Date 07-24-2006/16:05:12/8
Exposure analysis for 3 combined weeks: starting week 35 (of 52)
Exposure amounts adjusted for body weight
Dietary Residue file: C:\Calendexfiles\work\OPCRA\final\23July\water_OPCRA20.R98 Last saved: 7/23/2006 9:40:05 AM
Dietary Adjustment factor #2 used.
Dietary Matching File not used.
No non-dietary (residential) analysis
PRZM-EXAMS file: C:\Calendexfiles\work\OPCRA\final\water\OPCRA_RegA_NoOxon 6-5-06.PE1 Last saved:

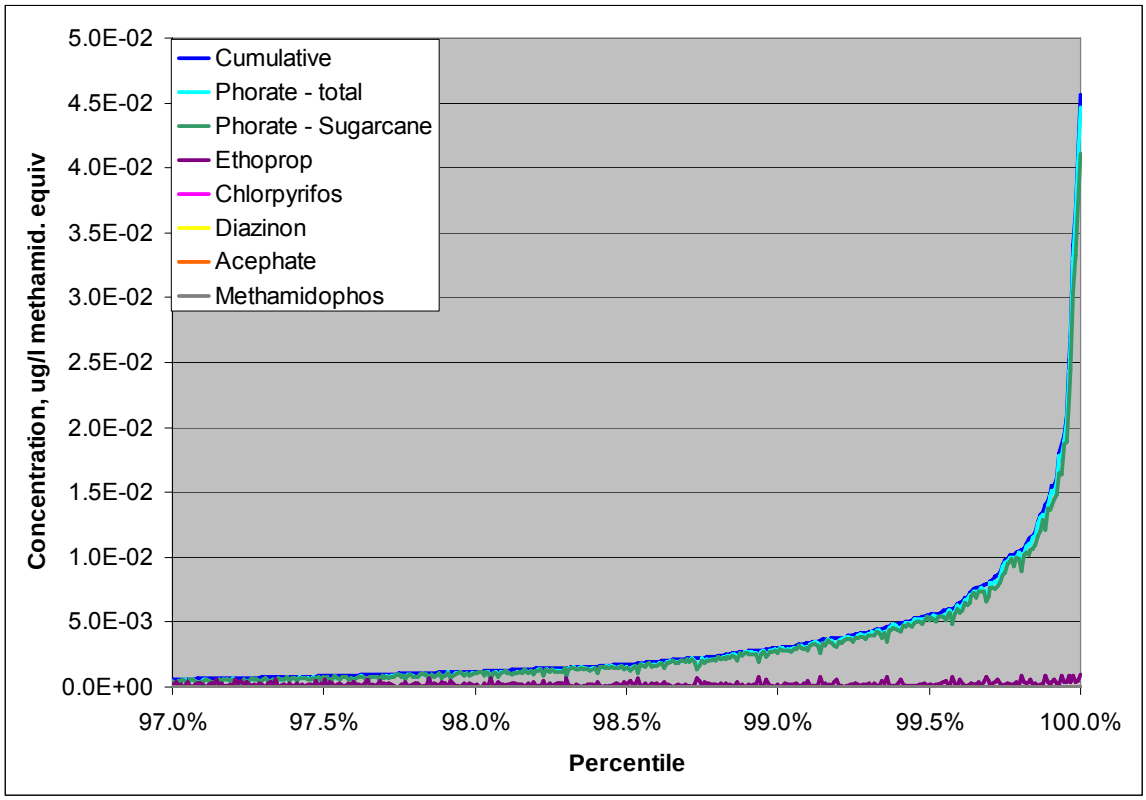
Demographics						Exposure (mg/ kg-Body Wt /da)			Water	
PID-HH#	Indiv	Itera-tion	Sex	Age	Body wt (kg)	Total	Dietary	Water	Conc. (mg/l)	Year

6/14/2006 2:21:06 PM
PE Analysis applied to Direct Water
PE Analysis applied to Indirect Water
NOEL Oral = 0.08 mg/kg-BodyWt/day

Lower and upper boundary percentiles entered as 99.800 100.000
Lower and upper exposure boundaries computed as: 0.000955 0.002335
Number of records in this file = 42

The cumulative peak for drinking water is driven largely by phorate and its sulfoxide and sulfone residues, which form in the environment. Figure II.G-3.3 shows the tail of the estimated OP cumulative distribution in drinking water sources, along with the component OP residues contributing to the cumulative exposure (all concentrations are in methamidophos equivalents). While both phorate and ethoprop are applied to sugarcane at the same time and can occur together in water, the cumulative OP concentrations (shown as a dark blue line in Figure II.G-3.3) are driven largely by phorate residues (shown as a light blue line). This reflects differences in the amounts of pesticide applied, fate and transport properties, as well as relative potency differences, between phorate residues and ethoprop. Further, the analysis indicates that the estimated cumulative OP residues in the upper tail of the distribution are driven largely by phorate use on sugarcane (shown as the green line in Figure II.G-3.3).

Figure II.G-3.3 Upper Percentiles of Frequency Distribution of Cumulative OP Concentrations (in Methamidophos Equivalents) With Component OP Residues.



3. Characterization of Phorate Concentrations in Drinking Water

a. Fate and Transport Modeling of Total Phorate Residues

Because evidence from literature studies indicate that the sulfoxide and sulfone transformation products of phorate are expected to be similar in toxicity to the parent compound, EPA simulated the fate and transport of the combined toxic residues. Degradation (hydrolysis, aerobic soil and aquatic metabolism) were calculated based on total (phorate + sulfoxide + sulfone) residues. In the field, the individual components will degrade at different rates. Phorate breaks down relatively quickly in water (aerobic aquatic metabolism half-life of <2 days). The sulfoxide has a half-life of 9 days and the sulfone 21 days. The half-life for the combined residues was ~50 days. This combined half-life appears to be skewed by the tail of the degradation profile, which is not well represented by a first-order degradation model. Thus, the phorate residues are likely to decline more rapidly than estimated by the half-life rate used in the exposure assessment.

EPA used the sorption coefficient of the most mobile of the three chemicals (K_{oc} of 91 for phorate sulfoxide). While this provides a protective exposure estimate, it will also lead to overestimates to the extent that the other components are less mobile.

b. Total Phorate Load in Water

The majority of OP and phorate use in the south Florida exposure scenario is on sugarcane. While only a relatively small fraction of the sugarcane acreage was treated with OP pesticides (10% of acres treated with phorate; 6% with ethoprop), this still accounts for a relatively large acreage compared to other uses in the area. The estimated 43,000 acres of sugarcane treated with phorate is still greater than the total combined acreage of the other OP use crops. The drinking water exposure assessment assumes that the entire crop area is treated at the same time. While this assumption is not unreasonable for smaller watersheds supplying small community water systems, it is less probable that all 43,000 acres of sugarcane will be treated at the same time.

As applications are spread out over time, the total phorate load carried to water as a result of any single runoff event will be less than estimated assuming the entire application occurs in the same day. Since the phorate residues are not expected to be persistent in water, degradation between runoff events not only spreads out the estimated peak concentrations, but should reduce the total load moving through the drinking water system at any time.

The Agency does not have any information that would allow it to quantifiably adjust the distribution and timing of application of phorate across the extent of treated sugarcane acreage in Florida. Thus, while we can qualitatively characterize the impact of spreading out the application, we cannot quantify it at this time.

c. Nature of Drinking Water Supply

Only a small number of surface water sources of drinking water occur in south Florida. Sugarcane is grown south of Lake Okeechobee in the Everglades Agricultural Area (EAA), and to the east into Palm Beach County. Three community water systems (CWS) draw from the southern end of Lake Okeechobee, and the city of West Palm Beach draws water from Clear Lake, which is fed in part by drainage water from the EAA. The agricultural areas in south Florida include extensive drainage canals and water retention structures. Thus, the drinking water exposure scenario for Region A better represents water being held in canals or retention bodies than in reservoirs that directly supply

the community water systems. Drainage canals from sugarcane fields are not used directly for drinking water, but water from drainage canals eventually feed water bodies used in southern Florida for drinking water supply.

Because the phorate residues degrade in water, any increase in holding time in retention structures or travel time in canals will result in some degradation and a lowering of residues in water. Additional dilution will occur where the drainage water flows into larger water bodies used for water supply. While the potential dilution effect is accounted for to a large extent by the percent crop area adjustment applied for this region, the decline in residues with travel time has not been taken into account.

d. Drinking Water Treatment Effects

Although the drinking water treatment studies documented in Appendices II.E.1 and II.E.2 (EPA, 2006a and 2006b) were designed only to determine the potential for oxon formation as a result of chlorination, they also indicate that the phorate residues (parent plus transformation products) are not likely to be stable as a result of chlorination. Phorate concentrations dropped to non-detectable levels within 1 hour of chlorination in benchtop jar tests (Appendices II.E.1 and II.E.2). Similarly, concentrations of phorate sulfoxide and sulfone also dropped to non-detectable levels shortly after chlorination. While phorate sulfoxide oxon was briefly detected in the lab studies, the oxon was not stable.

Thus, the overall phorate levels in drinking water in south Florida are likely to be much lower than estimated here.

G-4. Sensitivity Analysis: Acute Hazard Endpoints Compared to Single Day Food Estimates.

1. Background

The food component of the Organophosphorus Cumulative Risk Assessment (OP CRA) Update 2006 presented both single-day and 21-day exposure estimates for various age groups based on toxicity values derived from 21-day and longer (steady state) animal toxicity studies. As explained more fully in Chapter I.G, the Agency believes that the 21-day rolling average analysis better represents the cumulative risk to the OPs. The Agency further believes that the single day values compared with relative potency factors (RPFs) and points of departure (PoDs) derived from animal data representing steady state brain cholinesterase inhibition provide high end estimates using compounding conservative assumptions.

Although the Agency's OP CRA uses steady state brain cholinesterase data to extrapolate risk from 21-day rolling average exposure profiles, the Agency is concerned with the potential for peak exposures to OPs. Single chemical aggregate risk assessments include thorough analysis of acute exposure to individual OPs. The CRA is designed to evaluate the combined risk to many OPs. The Agency has conducted a sensitivity analysis where cumulative risks from single day food exposures were calculated using RPFs and PoD derived from acute toxicity studies in rat. The purpose of this analysis was:

1) to better understand the relationship between the results reported for the single-day and 21-day rolling average analyses compared with the steady state hazard data and;

2) to ensure that the CRA was protective of potential peak exposures to multiple OPs in food.

2. Approach

<u>The following analysis is meant only as a sensitivity analysis</u> and is not intended to replace the results presented in I.C and I.G for the 21-day rolling average analysis. The Agency only collected acute toxicity information for those OPs that most significantly contribute to food exposure for children 1-2 and 3-5 years old. Data from comparative cholinesterase studies where juvenile (post-natal day 11) or adult rats were exposed to an oral single dose were preferred when available.

Similar to that described in I.B for data from repeated dosing comparative cholinesterase studies, the OPCum Risk program was used to derive the estimates provided in II.G-4.1. In cases where the adult and pup data were adequately modeled with OPCum Risk, the adult BMD was used to derive the acute RPF with pup data used to derive the FQPA safety factor for acute dosing. This approach is similar to that used for the steady state, repeated dosing studies in I.B.

For four OPs, the pup data were adequately modeled with the OPCumRisk but the adult data were not. For these four, the pup data were used directly to estimate the acute RPF. It is preferred to derive RPFs from a uniform sex and life stage but for purposes of this sensitivity analysis, this is a reasonable approach.

BMD modeling was not attempted for some OPs, instead the acute value was estimated from either a NOAEL or LOAEL or an extrapolation between the NOAEL and LOAEL. For all other OPs not identified as contributors to the cumulative food exposure assessment, the toxicity information used in this acute analysis was the same as that reported for the steady state, repeated exposures. As such, the current analysis provides an upper bound on potential acute cumulative risks to the OPs.

Acute RPFs were calculated using methamidophos as the index chemical. RPFs were estimated based on the ratios of BMD_{10} or other endpoint as appropriate. The acute PoD was based on the methamidophos $BMDL_{10}$ of 0.22 mg/kg from acute brain cholinesterase inhibition in adult female rat.

These acute endpoints were incorporated into a single-day food assessment. The same sources of consumption information and residue data that were used in the single-day and 21-day food assessments discussed in Section I.C were included in this sensitivity analysis. Specifically dietary consumption information from USDA's Continuing Survey of Food Intake by Individuals (1994-1996/1998) and data on OP residues found in food from USDA's Pesticide Data Program (1994-2004) were used to assess the single-day food exposure.

Table II.G-4.1 Summary Table of Acute Endpoints from Adult or Juvenile Rats from Single Dosing Studies for Some OPs.

OP	Acute endpoint (mg/kg)	Source	FQPA SF	Acute RPF (methamidophos equivalents)
Azinphos methyl	0.44	BMD_{10} for female pups (see below)	1	0.59
Chlorpyrifos	1.1	Estimated from Zheng et al (2000) in neonates	1	0.24
Malathion	52.5	BMD_{10} for female pups from Reiss (2006)	1	0.0050
Methyl parathion	0.15	BMD_{10} for female pups (see below)	1	1.73
Acephate	0.29	BMD_{10} for female adult rats (see below)	1	0.90
Diazinon	0.63	BMD_{10} for female adult rats (see below)	2	0.41
Dimethoate	2.19	BMD_{10} for female adult rats (see below). Other BMD estimates from same study can be found in USEPA, 2004.	1	0.12
Disulfoton	0.138	BMD_{10} for female adult rats (see below)	1	1.88
Methamidophos	0.26	BMD_{10} for female adult rats (see below)	2	1.00
Omethoate	0.18	BMD_{10} for female adult rats from TXR No. 0052940, April 11, 2005	1	1.44
ODM	0.5	estimated from MRID 43929901	10	0.52
Phosmet	9	estimated from MRID 44673301	10	0.029
Phorate	0.75	estimated from MRID 44719901	10	0.35
Methidathion	1	LOAEL from MRID 43145901, 43145902	10	0.26
Chlorpyrifos methyl	16.2	steady state BMD_{10}	10	0.016

3. Results

In Chapter I.C, the margins of exposure (MOEs) at 95th, 99th, and 99.9th percentiles of exposure are reported for the 21-day and single-day food assessments based on steady state endpoints. These MOEs were reported for various age groups, the mostly highly exposed of which were children 1-2 and 3-5 years old. Briefly, the MOEs for the 21-day assessment are above or very close to the target of 100 at the 99.9th percentile of exposure for all age groups; the MOEs for the 95th and 99th percentiles of exposure are well above 100.

In the single day analyses (using steady state RPFs and PoDs), at the 95th and 99th percentiles of exposure the MOEs for all age groups are above 100. However for the single-day analyses (using steady state RPFs and PoDs), the MOEs at the 99.9th percentile of exposure do not reach the target value of 100 for any of the age groups. More specifically, the MOEs at the 99.9th percentile of exposure for children 1-2 and children 3-5 years old are 31 and 35, respectively. MOEs of 100 were reached at approximately the 99.3rd and 99.5th percentile of exposure for children 1-2 and 3-5 years old, respectively (see Chapter I.C for detailed reporting of the MOEs).

When the RPFs based on single-day acute endpoints are incorporated into the single-day exposure food assessment, the MOEs at the 99.9th percentile exceeded the target of 100 for all age groups except children 1-2 and 3-5 years old. The MOEs for these two most highly exposed age groups reached the target of 100 at approximately the 99.7th and 99.8th percentiles of exposure, respectively. It is important to note that for most OPs, the steady state RPFs are included in this sensitivity analysis. In the event that acute toxicity information were used for more OPs in this analysis, the MOEs would increase as would the percentile at which the MOEs reach 100.

Table II.G.4 2-4 provides a comparison of MOEs at 99.9th percentiles of exposure from the 21-day and single-day food assessments presented in Chapter I.C and the single-day food assessment described in this Appendix. Tables II.G.4 3 and II.G.4 4 provide similar comparisons of the MOEs at the 99th and 95th percentiles of exposure. Although three age groups are presented in these Tables, the MOEs for the all other age groups exceed the target MOE of 100 at the percentiles presented.

Table II.G-4.2 Cumulative Food Assessment MOEs at the 99.9th Percentile Exposure.

	21-Day Analysis Based on Steady State Endpoints	Single-Day Analysis Based on Steady State Endpoints	Single-Day Analysis Based on Single-Day Endpoints
Children 1-2 yrs	110	30	52
Children 3-5 yrs	99	34	63
Adults 20-49 yrs	280	75	130

Table II.G-4.3 Cumulative Food Assessment MOEs at the 99th Percentile Exposure.

	21-Day Analysis Based on Steady State Endpoints	Single-Day Analysis Based on Steady State Endpoints	Single-Day Analysis Based on Single-Day Endpoints
Children 1-2 yrs	250	130	200
Children 3-5 yrs	300	160	250
Adults 20-49 yrs	610	290	480

Table II.G-4.4 Cumulative Food Assessment MOEs at the 95th Percentile Exposure.

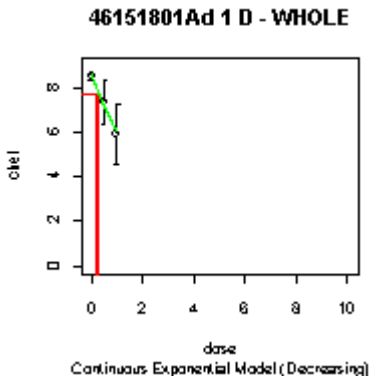
	21-Day Analysis Based on Steady State Endpoints	Single-Day Analysis Based on Steady-State Endpoints	Single-Day Analysis Based on Single-Day Endpoints
Children 1-2 yrs	550	440	610
Children 3-5 yrs	670	510	690
Adults 20-49 yrs	820	990	1400

4. Conclusion

In order to better characterize the single-day food exposure estimates, the Agency performed a sensitivity analysis that paired single day-exposure duration with single-day acute endpoints based on brain cholinesterase data. By incorporating endpoints from toxicity studies with exposure durations comparable to those being assessed in the food exposure, the Agency has a better understanding of the extent to which the use of steady state endpoints in the single-day food assessment overstates the risks of exposure to OPs. Based on this sensitivity analysis, the Agency concludes that 1) use of steady state endpoints in the single-day food assessment overestimates risk by almost 2-fold at the upper percentiles of exposure and 2) OP CRA was protective of potential peak exposures to multiple OPs in food.

5. BMD analysis for: Acephate

```
                    Acephate:1-D:BRAIN:F:WHOLE
                      Sun Feb 17 20:03:32 2002
               MRID: 46151801Ad   Guideline: NONGUIDELINE
               Continuous Exponential Model (Decreasing)
               Formula: chei = B + (A-B)*exp(-(m*dose)^g)

Variance Function: power

Highest 2 doses dropped from data set.


   The BMD corresponds to a dose that results in a 10% reduction in the
                    response relative to the control
    ------------------------------------------------------------------
                    Summary of Model Fitting Results

      AIC       BIC    logLik
114.57073 118.77432 -54.28537

Coefficients:
      Value Std.Error
A 8.6366705 0.5264088
m 0.3582992 0.0947503

Correlation:
          A         m
A 1.0000000 0.7728167
m 0.7728167 1.0000000

Approximate 95% confidence intervals

 Coefficients:
      lower      est.    upper
A 7.6229684 8.6366705 9.785175
m 0.2084456 0.3582992 0.615884

 Residual standard error:
   lower     est.    upper
1.433447 1.806305 2.442940

Degrees of freedom: 30 total; 28 residual
    ------------------------------------------------------------------
                            Goodness of Fit
 The chi-squared goodness-of-fit values should be taken as general
indications of fit only.  P-values are likely to be inaccurate to some
degree

Pearson Chi-Square Statistic: 0.2075 with 1 degrees of freedom.  P =
0.649

  dose  n chei Expected   sd   Exp.SD  X2 Resid.
1  0.0 10 8.53 8.636671 0.21 1.821972 -0.1851411
```



```
2  0.5 10 7.40 7.220091 1.44 1.529698  0.3719182
3  1.0 10 5.96 6.035858 1.90 1.284309 -0.1867796

    ------------------------------------------------------------------
                            BMD Computation

                     BMD = 0.2941:  BMDL = 0.2049

    ------------------------------------------------------------------
                            Potency Measures

A unit dose (1 mg/kg) would result in 100*exp(-Potency)% of background
activity

Potency: 0.3583
se: 0.09475
var=se^2: 0.008978
Per cent. of background at unit dose: 70
Per cent. of background at the highest dose: 70
ED50 (95% CI): 1.935 ( 1.152 , 3.248 )

ln(Potency) -1.026
se[log(Potency)]: 0.2644
se[log(Potency)]^2: 0.06993
```

Acephate:1-D:BRAIN:M:WHOLE
Sun Feb 17 20:05:00 2002
MRID: 46151801Ad Guideline: NONGUIDELINE
Continuous Exponential Model (Decreasing)
Formula: chei = B + (A-B)*exp(-(m*dose)^g)

Variance Function: power

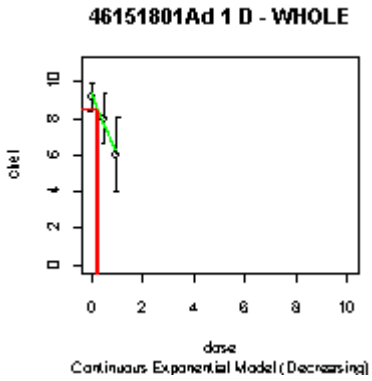
Highest 2 doses dropped from data set.

The BMD corresponds to a dose that results in a 10% reduction in the response relative to the control

---

Summary of Model Fitting Results

```
      AIC       BIC    logLik
139.48858 143.69217 -66.74429

Coefficients:
      Value Std.Error
A 9.4233756 0.8201802
m 0.4236354 0.1359193

Correlation:
          A         m
A 1.0000000 0.7704751
m 0.7704751 1.0000000

Approximate 95% confidence intervals

 Coefficients:
      lower      est.     upper
A 7.8845617 9.4233756 11.262517
m 0.2195680 0.4236354  0.817364

 Residual standard error:
   lower     est.    upper
2.213380 2.789110 3.772136

Degrees of freedom: 30 total; 28 residual
```



Goodness of Fit

The chi-squared goodness-of-fit values should be taken as general indications of fit only. P-values are likely to be inaccurate to some degree

Pearson Chi-Square Statistic: 0.415 with 1 degrees of freedom. P = 0.519

	dose	n	chei	Expected	sd	Exp.SD	X2 Resid.
1	0.0	10	9.19	9.423376	1.04	2.835597	-0.2602621
2	0.5	10	8.01	7.624568	1.89	2.317218	0.5259940
3	1.0	10	6.01	6.169131	2.85	1.893605	-0.2657450

BMD Computation

BMD = 0.2487: BMDL = 0.1628

Potency Measures

A unit dose (1 mg/kg) would result in 100*exp(-Potency)% of background activity

Potency: 0.4236
se: 0.1359
var=se^2: 0.01847
Per cent. of background at unit dose: 65
Per cent. of background at the highest dose: 65
ED50 (95% CI): 1.636 (0.8724 , 3.069)

ln(Potency) -0.8589
se[log(Potency)]: 0.3208
se[log(Potency)

Acephate:1-D:BRAIN:F:WHOLE
Sun Feb 17 20:06:14 2002
MRID: 46151801Pup Guideline: NONGUIDELINE
Continuous Exponential Model (Decreasing)
Formula: chei = B + (A-B)*exp(-(m*dose)^g)

Variance Function: power

The BMD corresponds to a dose that results in a 10% reduction in the response relative to the control

---

Summary of Model Fitting Results

AIC	BIC	logLik
91.79047	99.43856	-41.89524

Coefficients:

	Value	Std.Error
A	4.8229620	0.1653141
B	2.7338332	0.5168364
m	0.1831715	0.1177195

Correlation:

	A	B	m
A	1.0000000	0.5470928	0.6625012
B	0.5470928	1.0000000	0.9503303
m	0.6625012	0.9503303	1.0000000

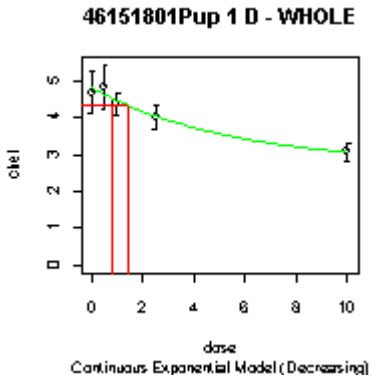
Approximate 95% confidence intervals

Coefficients:

	lower	est.	upper
A	4.50160020	4.8229620	5.1672654
B	1.86895853	2.7338332	3.9989351
m	0.05027613	0.1831715	0.6673504

Residual standard error:

lower	est.	upper
0.5610703	0.6739836	0.8442186



Degrees of freedom: 50 total; 47 residual

Goodness of Fit

The chi-squared goodness-of-fit values should be taken as general indications of fit only. P-values are likely to be inaccurate to some degree

Pearson Chi-Square Statistic: 1.695 with 2 degrees of freedom. P = 0.429

	dose	n	chei	Expected	sd	Exp.SD	X2 Resid.
1	0.0	10	4.70	4.822962	0.80	0.6680708	-0.58203428
2	0.5	10	4.86	4.640128	0.86	0.6432862	1.08085114
3	1.0	10	4.39	4.473295	0.42	0.6205997	-0.42443042
4	2.5	10	4.04	4.055401	0.45	0.5634268	-0.08643678
5	10.0	10	3.07	3.068384	0.36	0.4252122	0.01202137

```
-------------------------------------------------------------------
                        BMD Computation

                  BMD = 1.433:  BMDL = 0.846

-------------------------------------------------------------------
                        Potency Measures

A unit dose (1 mg/kg) would result in 100*exp(-Potency)% of background
activity

Potency: 0.1832
se: 0.1177
var=se^2: 0.01386
Per cent. of background at unit dose: 83
Per cent. of background at the highest dose: 16
ED50 (95% CI): 3.784 ( 1.074 , 13.34 )

ln(Potency) -1.697
se[log(Potency)]: 0.6427
se[log(Potency)]^2: 0.413
```

Acephate:1-D:BRAIN:M:WHOLE
Sun Feb 17 20:06:48 2002
MRID: 46151801Pup Guideline: NONGUIDELINE
Continuous Exponential Model (Decreasing)
Formula: chei = B + (A-B)*exp(-(m*dose)^g)

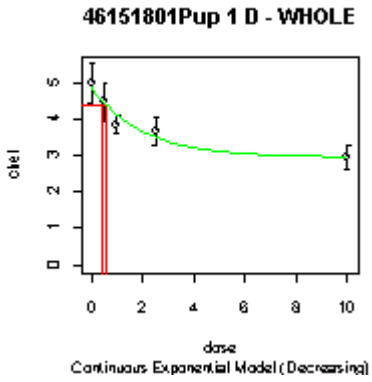
Variance Function: power

The BMD corresponds to a dose that results in a 10% reduction in the response relative to the control

---

Summary of Model Fitting Results

```
      AIC       BIC    logLik
 91.73380  99.38189 -41.86690

Coefficients:
      Value Std.Error
A 4.8538392 0.1916032
B 2.9464190 0.1488105
m 0.5017972 0.1441051

Correlation:
          A         B         m
A 1.0000000 0.1359877 0.5910295
B 0.1359877 1.0000000 0.5823909
m 0.5910295 0.5823909 1.0000000

Approximate 95% confidence intervals

 Coefficients:
      lower      est.     upper
A 4.4832911 4.8538392 5.2550135
B 2.6617570 2.9464190 3.2615241
m 0.2815946 0.5017972 0.8941948

 Residual standard error:
    lower      est.     upper
0.6092851 0.7319014 0.9167653

Degrees of freedom: 50 total; 47 residual
```



Goodness of Fit

The chi-squared goodness-of-fit values should be taken as general indications of fit only. P-values are likely to be inaccurate to some degree

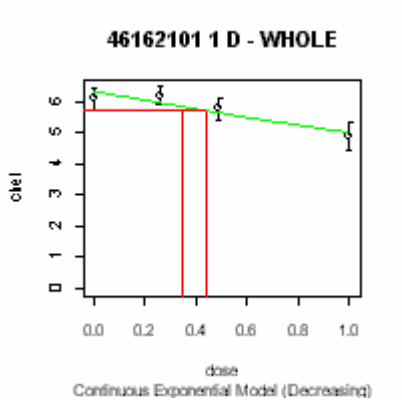
Pearson Chi-Square Statistic: 3.052 with 2 degrees of freedom. P = 0.217

	dose	n	chei	Expected	sd	Exp.SD	X2 Resid.
1	0.0	10	4.96	4.853839	0.75	0.7240145	0.4636783
2	0.5	10	4.47	4.430585	0.73	0.6536323	0.1906897
3	1.0	10	3.84	4.101250	0.35	0.6006885	-1.3753328
4	2.5	10	3.64	3.490454	0.53	0.5083676	0.9302434
5	10.0	10	2.93	2.959042	0.47	0.4409028	-0.2082983

```
------------------------------------------------------------------
                        BMD Computation

                BMD = 0.5852:  BMDL = 0.3935

------------------------------------------------------------------
                        Potency Measures

A unit dose (1 mg/kg) would result in 100*exp(-Potency)% of background
activity

Potency: 0.5018
se: 0.1441
var=se^2: 0.02077
Per cent. of background at unit dose: 61
Per cent. of background at the highest dose: 0.66
ED50 (95% CI): 1.381 ( 0.7868 , 2.425 )

ln(Potency) -0.6896
se[log(Potency)]: 0.2872
```
se[log(Potency)]^2: 0.08247

6. BMD analysis for: Azinphos methyl

```
                        Azinphos-methyl:1-D:BRAIN:F:WHOLE
                       Tue Jan 25 22:32:28 2005
                 MRID: 46162101   Guideline: NONGUIDELINE
               Continuous Exponential Model (Decreasing)
               Formula: chei = B + (A-B)*exp(-(m*dose)^g)

Variance Function: power


   The BMD corresponds to a dose that results in a 10% reduction in the
                    response relative to the control
    ------------------------------------------------------------------
                    Summary of Model Fitting Results

      AIC       BIC    logLik
 67.98541  73.05205 -30.99270

Coefficients:
      Value  Std.Error
A 6.3561429 0.14634233
m 0.2375225 0.04047062

Correlation:
          A         m
A 1.0000000 0.7634762
m 0.7634762 1.0000000

Approximate 95% confidence intervals

 Coefficients:
      lower      est.     upper
A 6.0666864 6.3561429 6.6594101
m 0.1682302 0.2375225 0.3353557

 Residual standard error:
    lower      est.     upper
0.4763423 0.5828629 0.7511810

Degrees of freedom: 40 total; 38 residual
    ------------------------------------------------------------------
                              Goodness of Fit
 The chi-squared goodness-of-fit values should be taken as general
indications of fit only.  P-values are likely to be inaccurate to some
degree

Pearson Chi-Square Statistic: 4.731 with 2 degrees of freedom.  P =
0.0939

  dose  n chei Expected  sd    Exp.SD  X2 Resid.
1 0.00 10  6.1 6.356143 0.5 0.5947195 -1.3619781
2 0.26 10  6.2 5.975489 0.4 0.5608027  1.2659842
3 0.49 10  5.8 5.657803 0.5 0.5324153  0.8445772
```



```
4 1.00 10  4.9 5.012322 0.6 0.4744902 -0.7485759

    ------------------------------------------------------------------
                              BMD Computation

                      BMD = 0.4436:  BMDL = 0.3465

    ------------------------------------------------------------------
                              Potency Measures

A unit dose (1 mg/kg) would result in 100*exp(-Potency)% of background
activity

Potency: 0.2375
se: 0.04047
var=se^2: 0.001638
Per cent. of background at unit dose: 79
Per cent. of background at the highest dose: 79
ED50 (95% CI): 2.918 ( 2.09 , 4.075 )

ln(Potency) -1.437
se[log(Potency)]: 0.1704
se[log(Potency)]^2: 0.02903
```

Azinphos-methyl:1-D:BRAIN:M:WHOLE
Tue Jan 25 22:32:43 2005
MRID: 46162101 Guideline: NONGUIDELINE
Continuous Exponential Model (Decreasing)
Formula: chei = B + (A-B)*exp(-(m*dose)^g)

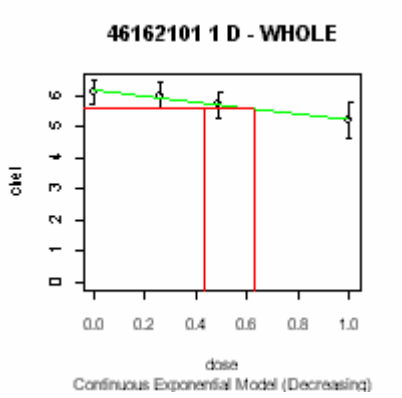
Variance Function: power

The BMD corresponds to a dose that results in a 10% reduction in the response relative to the control

---

Summary of Model Fitting Results

```
      AIC       BIC    logLik
 81.23741  86.30405 -37.61871

Coefficients:
      Value  Std.Error
A 6.1740066 0.16787774
m 0.1668837 0.04759997

Correlation:
          A         m
A 1.0000000 0.7648504
m 0.7648504 1.0000000

Approximate 95% confidence intervals

 Coefficients:
       lower      est.     upper
A 5.84334017 6.1740066 6.5233849
m 0.09367979 0.1668837 0.2972911

 Residual standard error:
    lower      est.     upper
0.5522574 0.6757542 0.8708973

Degrees of freedom: 40 total; 38 residual
```



Goodness of Fit

The chi-squared goodness-of-fit values should be taken as general indications of fit only. P-values are likely to be inaccurate to some degree

Pearson Chi-Square Statistic: 0.3202 with 2 degrees of freedom. P = 0.852

	dose	n	chei	Expected	sd	Exp.SD	X2 Resid.
1	0.00	10	6.1	6.174007	0.5	0.6833425	-0.34247732
2	0.26	10	6.0	5.911847	0.6	0.6546946	0.42579500
3	0.49	10	5.7	5.689230	0.6	0.6303551	0.05402769
4	1.00	10	5.2	5.225050	0.8	0.5795639	-0.13667817

BMD Computation

BMD = 0.6313: BMDL = 0.4297

Potency Measures

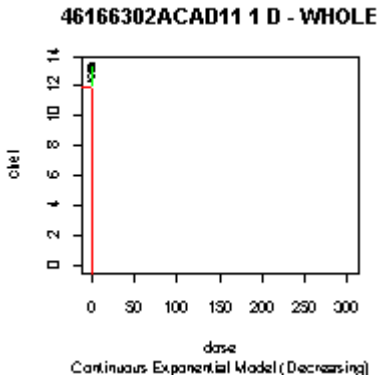
A unit dose (1 mg/kg) would result in 100*exp(-Potency)% of background activity

Potency: 0.1669
se: 0.0476
var=se^2: 0.002266
Per cent. of background at unit dose: 85
Per cent. of background at the highest dose: 85
ED50 (95% CI): 4.153 (2.375 , 7.264)

ln(Potency) -1.79
se[log(Potency)]: 0.2852
se[log(Potency)]^2: 0.08136

7. BMD analysis for: Diazinon

```
                        DIAZINON:1-D:BRAIN:F:WHOLE
                        Fri Jan 04 17:10:29 1980
              MRID: 46166302ACAD11   Guideline: NONGUIDELINE
                Continuous Exponential Model (Decreasing)
                Formula: chei = B + (A-B)*exp(-(m*dose)^g)

Variance Function: power

Highest 2 doses dropped from data set.


   The BMD corresponds to a dose that results in a 10% reduction in the
                    response relative to the control
    ------------------------------------------------------------------
                    Summary of Model Fitting Results

      AIC       BIC    logLik
12.023744 15.557906 -3.011872

Coefficients:
       Value  Std.Error
A 13.2366258 0.07685665
m  0.1662615 0.03335668

Correlation:
          A         m
A 1.0000000 0.6319335
m 0.6319335 1.0000000

Approximate 95% confidence intervals

 Coefficients:
       lower       est.      upper
A 13.0781907 13.2366258 13.3969802
m  0.1096711  0.1662615  0.2520528

 Residual standard error:
    lower      est.     upper
0.2267656 0.2932080 0.4149923

Degrees of freedom: 24 total; 22 residual
    ------------------------------------------------------------------
                              Goodness of Fit
 The chi-squared goodness-of-fit values should be taken as general
indications of fit only.  P-values are likely to be inaccurate to some
degree

Pearson Chi-Square Statistic: 0.8582 with 1 degrees of freedom.  P =
0.354

  dose n chei Expected  sd    Exp.SD   X2 Resid.
1 0.00 8 13.3 13.23663 0.2 0.2918109  0.61426556
2 0.03 8 13.1 13.17077 0.2 0.2903590 -0.68935997
```



```
3 0.30 8 12.6 12.59260 0.4 0.2776128  0.07541153

    ------------------------------------------------------------------
                              BMD Computation

                      BMD = 0.6337:  BMDL = 0.4765

    ------------------------------------------------------------------
                              Potency Measures

A unit dose (1 mg/kg) would result in 100*exp(-Potency)% of background
activity

Potency: 0.1663
se: 0.03336
var=se^2: 0.001113
Per cent. of background at unit dose: 85
Per cent. of background at the highest dose: 95
ED50 (95% CI): 4.169 ( 2.814 , 6.177 )

ln(Potency) -1.794
se[log(Potency)]: 0.2006
se[log(Potency)]^2: 0.04025
```

DIAZINON:1-D:BRAIN:M:WHOLE
Fri Jan 04 17:10:41 1980
MRID: 46166302ACAD11 Guideline: NONGUIDELINE
Continuous Exponential Model (Decreasing)
Formula: chei = B + (A-B)*exp(-(m*dose)^g)

Variance Function: power

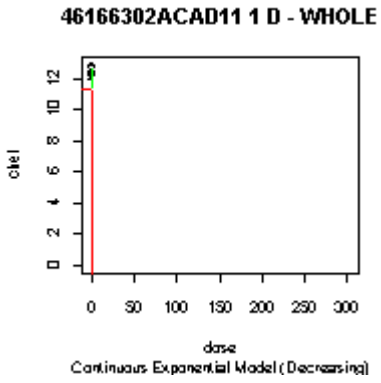
Highest 2 doses dropped from data set.

The BMD corresponds to a dose that results in a 10% reduction in the response relative to the control

---

Summary of Model Fitting Results

```
     AIC      BIC   logLik
3.077858 6.612020 1.461071

Coefficients:
       Value  Std.Error
A 12.5768854 0.06336178
m  0.1052754 0.02894230

Correlation:
          A         m
A 1.0000000 0.6319335
m 0.6319335 1.0000000

Approximate 95% confidence intervals

 Coefficients:
        lower       est.      upper
A 12.44616514 12.5768854 12.7089785
m  0.05952703  0.1052754  0.1861827

 Residual standard error:
    lower      est.     upper
0.1878795 0.2429283 0.3438288

Degrees of freedom: 24 total; 22 residual
```



Goodness of Fit

The chi-squared goodness-of-fit values should be taken as general indications of fit only. P-values are likely to be inaccurate to some degree

Pearson Chi-Square Statistic: 4.744 with 1 degrees of freedom. P = 0.0294

	dose	n	chei	Expected	sd	Exp.SD	X2 Resid.
1	0.00	8	12.7	12.57689	0.3	0.2405733	1.4474623
2	0.03	8	12.4	12.53723	0.1	0.2398147	-1.6184846
3	0.30	8	12.2	12.18588	0.2	0.2330941	0.1713184

BMD Computation

BMD = 1.001: BMDL = 0.6892

Potency Measures

A unit dose (1 mg/kg) would result in 100*exp(-Potency)% of background activity

Potency: 0.1053
se: 0.02894
var=se^2: 0.0008377
Per cent. of background at unit dose: 90
Per cent. of background at the highest dose: 97
ED50 (95% CI): 6.584 (3.841 , 11.29)

ln(Potency) -2.251
se[log(Potency)]: 0.2749
se[log(Potency)]^2: 0.07558

DIAZINON:1-D:BRAIN:F:WHOLE
Fri Jan 04 17:10:54 1980
MRID: 46166302ACPU11 Guideline: NONGUIDELINE
Continuous Exponential Model (Decreasing)
Formula: chei = B + (A-B)*exp(-(m*dose)^g)

Variance Function: power

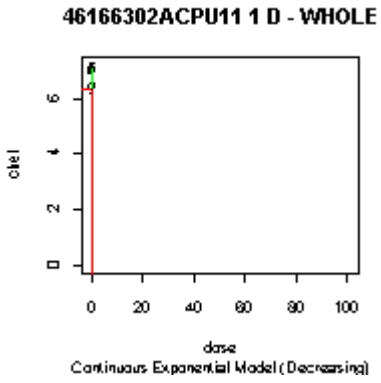
Highest 2 doses dropped from data set.

The BMD corresponds to a dose that results in a 10% reduction in the response relative to the control

---

Summary of Model Fitting Results

```
       AIC        BIC     logLik
-12.586972  -9.052810   9.293486

Coefficients:
      Value  Std.Error
A 7.0868338 0.04691799
m 0.3406463 0.03803346

Correlation:
          A         m
A 1.0000000 0.6319335
m 0.6319335 1.0000000

Approximate 95% confidence intervals

 Coefficients:
      lower      est.     upper
A 6.9901967 7.0868338 7.1848067
m 0.2702358 0.3406463 0.4294024

 Residual standard error:
    lower      est.     upper
0.1380279 0.1784701 0.2525979

Degrees of freedom: 24 total; 22 residual
```



Goodness of Fit

The chi-squared goodness-of-fit values should be taken as general indications of fit only. P-values are likely to be inaccurate to some degree

Pearson Chi-Square Statistic: 0.1007 with 1 degrees of freedom. P = 0.751

	dose	n	chei	Expected	sd	Exp.SD	X2 Resid.
1	0.00	8	7.1	7.086834	0.2	0.1781391	0.20904876
2	0.03	8	7.0	7.014779	0.1	0.1763279	-0.23707302
3	0.30	8	6.4	6.398380	0.2	0.1608337	0.02849558

BMD Computation

BMD = 0.3093: BMDL = 0.2613

Potency Measures

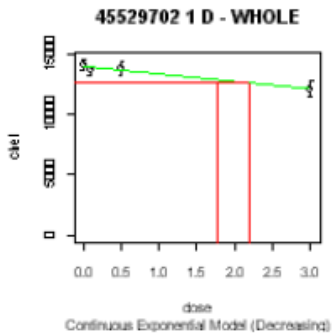
A unit dose (1 mg/kg) would result in 100*exp(-Potency)% of background activity

Potency: 0.3406
se: 0.03803
var=se^2: 0.001447
Per cent. of background at unit dose: 71
Per cent. of background at the highest dose: 90
ED50 (95% CI): 2.035 (1.635 , 2.533)

ln(Potency) -1.077
se[log(Potency)]: 0.1117
se[log(Potency)]^2: 0.01247

8. BMD analysis for: Dimethoate

```
                    DIMETHOATE:1-D:BRAIN:F:WHOLE
                      Wed Aug 18 20:21:06 2004
                MRID: 45529702   Guideline: NONGUIDELINE
               Continuous Exponential Model (Decreasing)
               Formula: chei = B + (A-B)*exp(-(m*dose)^g)

Variance Function: power


   The BMD corresponds to a dose that results in a 10% reduction in the
                        response relative to the control
    ------------------------------------------------------------------
                        Summary of Model Fitting Results

      AIC       BIC    logLik
 511.0838  515.4810 -252.5419

Coefficients:
         Value     Std.Error
A 1.400226e+04 1.530550e+02
m 4.801487e-02 7.186638e-03

Correlation:
          A         m
A 1.0000000 0.5913828
m 0.5913828 1.0000000

Approximate 95% confidence intervals

 Coefficients:
         lower          est.         upper
A 1.369314e+04 1.400226e+04 1.431835e+04
m 3.536891e-02 4.801487e-02 6.518233e-02

 Residual standard error:
   lower     est.    upper
563.8050 705.5395 943.0758

Degrees of freedom: 32 total; 30 residual
    ------------------------------------------------------------------
                              Goodness of Fit
 The chi-squared goodness-of-fit values should be taken as general
indications of fit only.  P-values are likely to be inaccurate to some
degree

Pearson Chi-Square Statistic: 2.517 with 2 degrees of freedom.  P =
0.284

  dose n      chei Expected       sd   Exp.SD   X2 Resid.
1  0.0 8 14150.00 14002.26 554.8488 698.0731  0.59861865
2  0.1 8 13625.00 13935.19 444.8114 694.7413 -1.26283056
3  0.5 8 13850.00 13670.10 687.1265 681.5724  0.74655058
4  3.0 8 12106.25 12123.84 826.5408 604.7383 -0.08228062
```



BMD Computation

BMD = 2.194: BMDL = 1.761

Potency Measures

A unit dose (1 mg/kg) would result in 100*exp(-Potency)% of background activity

Potency: 0.04801
se: 0.007187
var=se^2: 5.165e-05
Per cent. of background at unit dose: 95
Per cent. of background at the highest dose: 87
ED50 (95% CI): 14.44 (10.77 , 19.36)

ln(Potency) -3.036
se[log(Potency)]: 0.1497
se[log(Potency)]^2: 0.0224

DIMETHOATE:1-D:BRAIN:M:WHOLE
Wed Aug 18 20:21:12 2004
MRID: 45529702 Guideline: NONGUIDELINE
Continuous Exponential Model (Decreasing)
Formula: chei = B + (A-B)*exp(-(m*dose)^g)

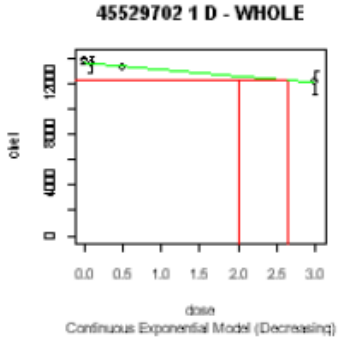
Variance Function: power

The BMD corresponds to a dose that results in a 10% reduction in the response relative to the control

---

Summary of Model Fitting Results

```
      AIC       BIC    logLik
 515.1097  519.5069 -254.5549
```



Coefficients:

```
         Value     Std.Error
A 1.365711e+04 161.84622769
m 3.992759e-02   0.00778649
```

Correlation:

```
          A         m
A 1.0000000 0.5916283
m 0.5916283 1.0000000
```

Approximate 95% confidence intervals

Coefficients:

```
         lower         est.         upper
A 1.333055e+04 1.365711e+04 1.399168e+04
m 2.681049e-02 3.992759e-02 5.946226e-02
```

Residual standard error:

```
   lower     est.    upper
595.7456 745.5096 996.5029
```

Degrees of freedom: 32 total; 30 residual

Goodness of Fit

The chi-squared goodness-of-fit values should be taken as general indications of fit only. P-values are likely to be inaccurate to some degree

Pearson Chi-Square Statistic: 0.4635 with 2 degrees of freedom. P = 0.793

```
  dose n      chei Expected        sd   Exp.SD   X2 Resid.
1  0.0 8 13793.75 13657.11  247.0360 738.2140  0.52351076
2  0.1 8 13543.75 13602.69  802.4238 735.2619 -0.22674697
3  0.5 8 13293.75 13387.17  241.1838 723.5707 -0.36517900
4  3.0 8 12131.25 12115.41 1096.4024 654.5977  0.06846042
```

BMD Computation

BMD = 2.639: BMDL = 1.998

Potency Measures

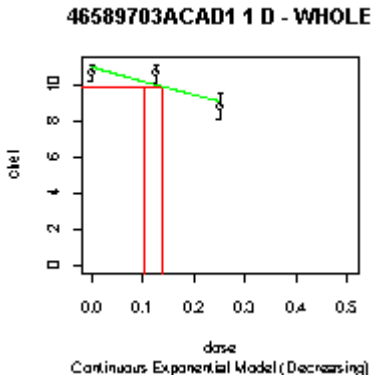
A unit dose (1 mg/kg) would result in 100*exp(-Potency)% of background activity

Potency: 0.03993
se: 0.007786
var=se^2: 6.063e-05
Per cent. of background at unit dose: 96
Per cent. of background at the highest dose: 89
ED50 (95% CI): 17.36 (11.85 , 25.44)

ln(Potency) -3.221
se[log(Potency)]: 0.195
se[log(Potency)]^2: 0.03803

9. BMD analysis for: Disulfoton

```
                    DISULFOTON:1-D:BRAIN:F:WHOLE
                       Fri Jan 04 18:43:46 1980
              MRID: 46589703ACAD1   Guideline: NONGUIDELINE
                Continuous Exponential Model (Decreasing)
                Formula: chei = B + (A-B)*exp(-(m*dose)^g)

Variance Function: power

Highest 1 doses dropped from data set.


   The BMD corresponds to a dose that results in a 10% reduction in the
                       response relative to the control
    ------------------------------------------------------------------
                       Summary of Model Fitting Results

      AIC       BIC    logLik
 43.86740  46.53852 -18.93370

Coefficients:
      Value Std.Error
A 11.084294 0.2999007
m  0.762279 0.1683987

Correlation:
          A         m
A 1.0000000 0.7723353
m 0.7723353 1.0000000

Approximate 95% confidence intervals

 Coefficients:
       lower      est.     upper
A 10.4664220 11.084294 11.738641
m  0.4772279  0.762279  1.217593

 Residual standard error:
    lower      est.     upper
0.5830565 0.7828680 1.1914695

Degrees of freedom: 18 total; 16 residual
    ------------------------------------------------------------------
                              Goodness of Fit
 The chi-squared goodness-of-fit values should be taken as general
indications of fit only.  P-values are likely to be inaccurate to some
degree

Pearson Chi-Square Statistic: 6.682 with 1 degrees of freedom.  P =
0.00974

   dose n  chei  Expected    sd    Exp.SD X2 Resid.
1 0.000 6 10.74 11.084294 0.423 0.8038437 -1.049140
2 0.125 6 10.71 10.076886 0.500 0.7347869  2.110553
```



```
3 0.250 6  8.87  9.161037 0.712 0.6716626 -1.061385

    ---------------------------------------------------------------
                            BMD Computation

                    BMD = 0.1382:  BMDL = 0.1014

    ---------------------------------------------------------------
                            Potency Measures

A unit dose (1 mg/kg) would result in 100*exp(-Potency)% of background
activity

Potency: 0.7623
se: 0.1684
var=se^2: 0.02836
Per cent. of background at unit dose: 47
Per cent. of background at the highest dose: 83
ED50 (95% CI): 0.9093 ( 0.5897 , 1.402 )

ln(Potency) -0.2714
se[log(Potency)]: 0.2209
se[log(Potency)]^2: 0.0488
```

DISULFOTON:1-D:BRAIN:M:WHOLE
Fri Jan 04 18:43:53 1980
MRID: 46589703ACAD1 Guideline: NONGUIDELINE
Continuous Exponential Model (Decreasing)
Formula: chei = B + (A-B)*exp(-(m*dose)^g)

Variance Function: power

The BMD corresponds to a dose that results in a 10% reduction in the response relative to the control

---

Summary of Model Fitting Results

AIC	BIC	logLik
51.32418	54.85835	-22.66209

Coefficients:

	Value	Std.Error
A	11.9124247	0.24419930
m	0.8093126	0.07207062

Correlation:

	A	m
A	1.0000000	0.7614023
m	0.7614023	1.0000000

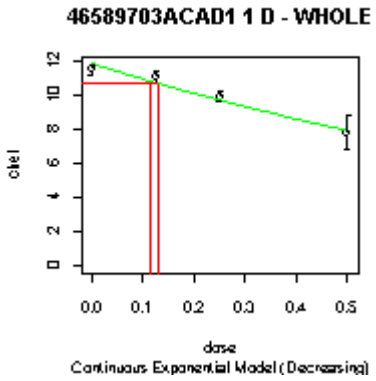
Approximate 95% confidence intervals

Coefficients:

	lower	est.	upper
A	11.4166006	11.9124247	12.42978
m	0.6728372	0.8093126	0.97347

Residual standard error:

lower	est.	upper
0.5805750	0.7506838	1.0624814



Degrees of freedom: 24 total; 22 residual

Goodness of Fit

The chi-squared goodness-of-fit values should be taken as general indications of fit only. P-values are likely to be inaccurate to some degree

Pearson Chi-Square Statistic: 3.568 with 2 degrees of freedom. P = 0.168

	dose	n	chei	Expected	sd	Exp.SD	X2 Resid.
1	0.000	6	11.54	11.912425	0.300	0.7701785	-1.1844664
2	0.125	6	11.08	10.766268	0.323	0.6988619	1.0996225
3	0.250	6	9.92	9.730388	0.266	0.6341490	0.7324017
4	0.500	6	7.81	7.948042	0.926	0.5221452	-0.6475853

BMD Computation

BMD = 0.1302: BMDL = 0.1136

Potency Measures

A unit dose (1 mg/kg) would result in 100*exp(-Potency)% of background activity

Potency: 0.8093
se: 0.07207
var=se^2: 0.005194
Per cent. of background at unit dose: 45
Per cent. of background at the highest dose: 67
ED50 (95% CI): 0.8565 (0.7193 , 1.02)

ln(Potency) -0.2116
se[log(Potency)]: 0.08905
se[log(Potency)]^2: 0.00793

DISULFOTON:1-D:BRAIN:F:WHOLE
Fri Jan 04 18:44:04 1980
MRID: 46589704ACPU1 Guideline: NONGUIDELINE
Continuous Exponential Model (Decreasing)
Formula: chei = B + (A-B)*exp(-(m*dose)^g)

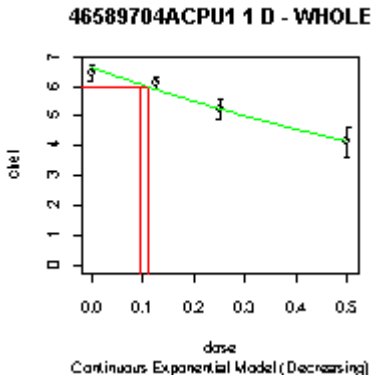
Variance Function: power

The BMD corresponds to a dose that results in a 10% reduction in the response relative to the control

---

Summary of Model Fitting Results

```
      AIC       BIC    logLik
 73.55314  78.61978 -33.77657

Coefficients:
      Value  Std.Error
A 6.6436319 0.17322549
m 0.9404764 0.09151811

Correlation:
          A         m
A 1.0000000 0.7619614
m 0.7619614 1.0000000

Approximate 95% confidence intervals

 Coefficients:
      lower      est.    upper
A 6.3020495 6.6436319 7.003729
m 0.7723146 0.9404764 1.145253

 Residual standard error:
    lower      est.     upper
0.5642684 0.6904511 0.8898384

Degrees of freedom: 40 total; 38 residual
```



Goodness of Fit

The chi-squared goodness-of-fit values should be taken as general indications of fit only. P-values are likely to be inaccurate to some degree

Pearson Chi-Square Statistic: 1.927 with 2 degrees of freedom. P = 0.382

	dose	n	chei	Expected	sd	Exp.SD	X2 Resid.
1	0.000	10	6.47	6.643632	0.388	0.7057578	-0.7779896
2	0.125	10	6.13	5.906771	0.280	0.6293962	1.1215727
3	0.250	10	5.23	5.251636	0.508	0.5612968	-0.1218960
4	0.500	10	4.12	4.151296	0.732	0.4464055	-0.2216976

BMD Computation

BMD = 0.112: BMDL = 0.09657

Potency Measures

A unit dose (1 mg/kg) would result in 100*exp(-Potency)% of background activity

Potency: 0.9405
se: 0.09152
var=se^2: 0.008376
Per cent. of background at unit dose: 39
Per cent. of background at the highest dose: 62
ED50 (95% CI): 0.737 (0.609 , 0.8919)

ln(Potency) -0.06137
se[log(Potency)]: 0.09731
se[log(Potency)]^2: 0.009469

DISULFOTON:1-D:BRAIN:M:WHOLE
Fri Jan 04 18:44:12 1980
MRID: 46589704ACPU1 Guideline: NONGUIDELINE
Continuous Exponential Model (Decreasing)
Formula: chei = B + (A-B)*exp(-(m*dose)^g)

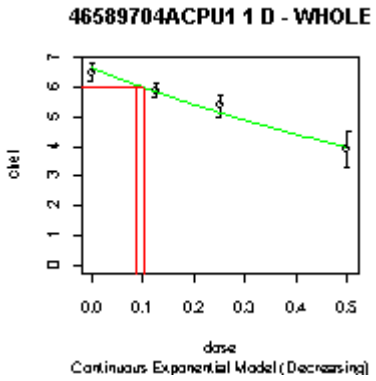
Variance Function: power

The BMD corresponds to a dose that results in a 10% reduction in the response relative to the control

---

Summary of Model Fitting Results

```
      AIC       BIC    logLik
 86.02089  91.08752 -40.01044

Coefficients:
     Value Std.Error
A 6.668492 0.2059587
m 1.033329 0.1089400

Correlation:
         A        m
A 1.000000 0.760291
m 0.760291 1.000000

Approximate 95% confidence intervals

 Coefficients:
      lower     est.    upper
A 6.2643172 6.668492 7.098744
m 0.8347373 1.033329 1.279168

 Residual standard error:
    lower      est.     upper
0.6719825 0.8222525 1.0597012

Degrees of freedom: 40 total; 38 residual
```



Goodness of Fit

The chi-squared goodness-of-fit values should be taken as general indications of fit only. P-values are likely to be inaccurate to some degree

Pearson Chi-Square Statistic: 2.08 with 2 degrees of freedom. P = 0.354

	dose	n	chei	Expected	sd	Exp.SD	X2 Resid.
1	0.000	10	6.49	6.668492	0.416	0.8375500	-0.6739183
2	0.125	10	5.90	5.860457	0.369	0.7404007	0.1688910
3	0.250	10	5.38	5.150333	0.538	0.6545200	1.1096240
4	0.500	10	3.88	3.977800	0.859	0.5114876	-0.6046525

BMD Computation

BMD = 0.102: BMDL = 0.08689

Potency Measures

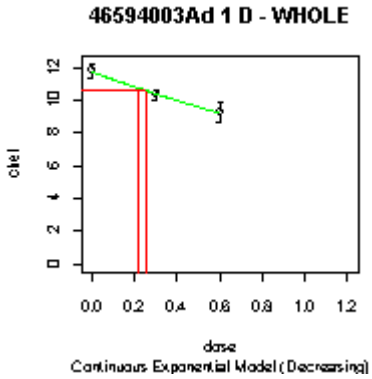
A unit dose (1 mg/kg) would result in 100*exp(-Potency)% of background activity

Potency: 1.033
se: 0.1089
var=se^2: 0.01187
Per cent. of background at unit dose: 36
Per cent. of background at the highest dose: 60
ED50 (95% CI): 0.6708 (0.5456 , 0.8248)

ln(Potency) 0.03279
se[log(Potency)]: 0.1054
se[log(Potency)]^2: 0.01111

10. BMD analysis for: Methamidophos

```
                    Methamidophos:1-D:BRAIN:F:WHOLE
                        Sun Feb 17 20:34:28 2002
                MRID: 46594003Ad   Guideline: NONGUIDELINE
                Continuous Exponential Model (Decreasing)
                Formula: chei = B + (A-B)*exp(-(m*dose)^g)

Variance Function: power

Highest 1 doses dropped from data set.


   The BMD corresponds to a dose that results in a 10% reduction in the
                    response relative to the control
    ------------------------------------------------------------------
                    Summary of Model Fitting Results

      AIC       BIC    logLik
 27.83708  30.50820 -10.91854

Coefficients:
       Value  Std.Error
A 11.7415463 0.19811091
m  0.4025792 0.04353016

Correlation:
          A         m
A 1.0000000 0.7750096
m 0.7750096 1.0000000

Approximate 95% confidence intervals

 Coefficients:
       lower       est.      upper
A 11.3289921 11.7415463 12.1691240
m  0.3201118  0.4025792  0.5062919

 Residual standard error:
    lower      est.     upper
0.3972568 0.5333953 0.8117898

Degrees of freedom: 18 total; 16 residual
    ------------------------------------------------------------------
                            Goodness of Fit
 The chi-squared goodness-of-fit values should be taken as general
indications of fit only.  P-values are likely to be inaccurate to some
degree

Pearson Chi-Square Statistic: 0.299 with 1 degrees of freedom.  P =
0.585

  dose n  chei  Expected    sd    Exp.SD  X2 Resid.
1  0.0 6 11.79 11.741546 0.462 0.5316938  0.2232240
```



```
2  0.3 6 10.32 10.405763 0.245 0.4707343 -0.4462707
3  0.6 6  9.26  9.221945 0.606 0.4167640  0.2236627

    ------------------------------------------------------------------
                            BMD Computation

                     BMD = 0.2617:  BMDL = 0.2222

    ------------------------------------------------------------------
                            Potency Measures

A unit dose (1 mg/kg) would result in 100*exp(-Potency)% of background
activity

Potency: 0.4026
se: 0.04353
var=se^2: 0.001895
Per cent. of background at unit dose: 67
Per cent. of background at the highest dose: 79
ED50 (95% CI): 1.722 ( 1.393 , 2.128 )

ln(Potency) -0.9099
se[log(Potency)]: 0.1081
se[log(Potency)]^2: 0.01169
```

Methamidophos:1-D:BRAIN:M:WHOLE
Sun Feb 17 20:35:03 2002
MRID: 46594003Ad Guideline: NONGUIDELINE
Continuous Exponential Model (Decreasing)
Formula: chei = B + (A-B)*exp(-(m*dose)^g)

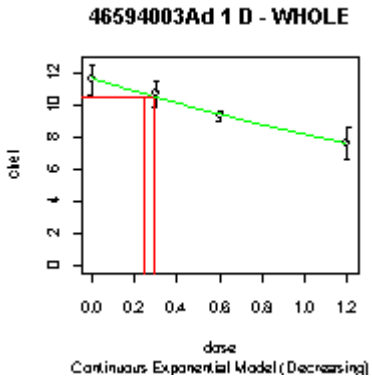
Variance Function: power

The BMD corresponds to a dose that results in a 10% reduction in the response relative to the control

---

Summary of Model Fitting Results

```
      AIC       BIC    logLik
 60.62975  64.16391 -27.31488

Coefficients:
       Value  Std.Error
A 11.6774231 0.30115998
m  0.3599319 0.03754709

Correlation:
         A        m
A 1.000000 0.763505
m 0.763505 1.000000

Approximate 95% confidence intervals

 Coefficients:
       lower       est.      upper
A 11.0692642 11.6774231 12.3189950
m  0.2899110  0.3599319  0.4468645

 Residual standard error:
    lower      est.     upper
0.7306618 0.9447461 1.3371477

Degrees of freedom: 24 total; 22 residual
```



Goodness of Fit

The chi-squared goodness-of-fit values should be taken as general indications of fit only. P-values are likely to be inaccurate to some degree

Pearson Chi-Square Statistic: 0.5066 with 2 degrees of freedom. P = 0.776

	dose	n	chei	Expected	sd	Exp.SD	X2 Resid.
1	0.0	6	11.58	11.677423	0.92	0.9520748	-0.25064938
2	0.3	6	10.68	10.482192	0.81	0.8549987	0.56670237
3	0.6	6	9.30	9.409297	0.31	0.7678208	-0.34867669
4	1.2	6	7.59	7.581712	0.94	0.6192252	0.03278316

BMD Computation

BMD = 0.2927: BMDL = 0.2499

Potency Measures

A unit dose (1 mg/kg) would result in 100*exp(-Potency)% of background activity

Potency: 0.3599
se: 0.03755
var=se^2: 0.00141
Per cent. of background at unit dose: 70
Per cent. of background at the highest dose: 65
ED50 (95% CI): 1.926 (1.57 , 2.363)

ln(Potency) -1.022
se[log(Potency)]: 0.1043
se[log(Potency)]^2: 0.01088

Methamidophos:1-D:BRAIN:F:WHOLE
Sun Feb 17 20:35:35 2002
MRID: 46594004Pup Guideline: NONGUIDELINE
Continuous Exponential Model (Decreasing)
Formula: chei = B + (A-B)*exp(-(m*dose)^g)

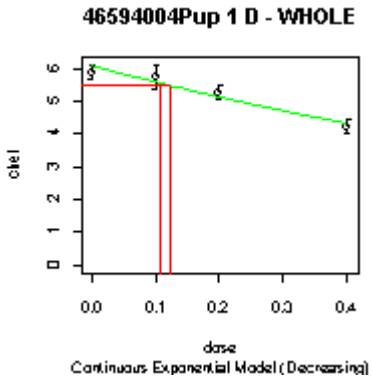
Variance Function: power

The BMD corresponds to a dose that results in a 10% reduction in the response relative to the control

---

Summary of Model Fitting Results

```
      AIC       BIC    logLik
 41.32496  46.31564 -17.66248

Coefficients:
      Value  Std.Error
A 6.0844265 0.11060609
m 0.8573064 0.08206989

Correlation:
          A         m
A 1.0000000 0.7565147
m 0.7565147 1.0000000

Approximate 95% confidence intervals

 Coefficients:
      lower      est.    upper
A 5.8643944 6.0844265 6.312714
m 0.7061503 0.8573064 1.040818

 Residual standard error:
    lower      est.     upper
0.3556643 0.4362566 0.5644058

Degrees of freedom: 39 total; 37 residual
```



Goodness of Fit

The chi-squared goodness-of-fit values should be taken as general indications of fit only. P-values are likely to be inaccurate to some degree

Pearson Chi-Square Statistic: 5.558 with 2 degrees of freedom. P = 0.0621

	dose	n	chei	Expected	sd	Exp.SD	X2 Resid.
1	0.0	10	5.88	6.084427	0.299	0.4487305	-1.4406276
2	0.1	10	5.74	5.584539	0.543	0.4134931	1.1889237
3	0.2	10	5.26	5.125721	0.299	0.3810228	1.1144414
4	0.4	9	4.22	4.318076	0.289	0.3235313	-0.9094258

BMD Computation

BMD = 0.1229: BMDL = 0.1062

Potency Measures

A unit dose (1 mg/kg) would result in 100*exp(-Potency)% of background activity

Potency: 0.8573
se: 0.08207
var=se^2: 0.006735
Per cent. of background at unit dose: 42
Per cent. of background at the highest dose: 71
ED50 (95% CI): 0.8085 (0.6702 , 0.9754)

ln(Potency) -0.154
se[log(Potency)]: 0.09573
se[log(Potency)]^2: 0.009164

Methamidophos:1-D:BRAIN:M:WHOLE
Sun Feb 17 20:36:06 2002
MRID: 46594004Pup Guideline: NONGUIDELINE
Continuous Exponential Model (Decreasing)
Formula: chei = B + (A-B)*exp(-(m*dose)^g)

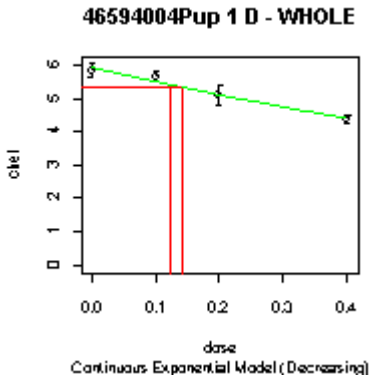
Variance Function: power

The BMD corresponds to a dose that results in a 10% reduction in the response relative to the control

---

Summary of Model Fitting Results

```
      AIC       BIC    logLik
15.656566 20.723205 -4.828283

Coefficients:
      Value  Std.Error
A 5.9354948 0.07809821
m 0.7491898 0.05757268

Correlation:
          A         m
A 1.0000000 0.7628871
m 0.7628871 1.0000000

Approximate 95% confidence intervals

 Coefficients:
      lower      est.     upper
A 5.7794803 5.9354948 6.0957208
m 0.6412533 0.7491898 0.8752943

 Residual standard error:
    lower      est.     upper
0.2558400 0.3130514 0.4034538

Degrees of freedom: 40 total; 38 residual
```



Goodness of Fit

The chi-squared goodness-of-fit values should be taken as general indications of fit only. P-values are likely to be inaccurate to some degree

Pearson Chi-Square Statistic: 3.792 with 2 degrees of freedom. P = 0.150

	dose	n	chei	Expected	sd	Exp.SD	X2 Resid.
1	0.0	10	5.82	5.935495	0.293	0.3185202	-1.146635272
2	0.1	10	5.65	5.507063	0.196	0.2959672	1.527220781
3	0.2	10	5.11	5.109556	0.409	0.2750110	0.005110363
4	0.4	10	4.37	4.398548	0.131	0.2374451	-0.380199278

BMD Computation

BMD = 0.1406: BMDL = 0.1249

Potency Measures

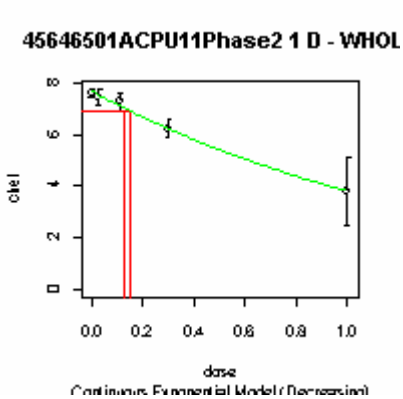
A unit dose (1 mg/kg) would result in 100*exp(-Potency)% of background activity

Potency: 0.7492
se: 0.05757
var=se^2: 0.003315
Per cent. of background at unit dose: 47
Per cent. of background at the highest dose: 74
ED50 (95% CI): 0.9252 (0.7958 , 1.076)

ln(Potency) -0.2888
se[log(Potency)]: 0.07685
se[log(Potency)]^2: 0.005905

11. BMD analysis for: Methyl parathion

```
                METHYL PARATHION:1-D:BRAIN:F:WHOLE
                      Fri Jan 04 14:23:23 1980
          MRID: 45646501ACPU11Phase2   Guideline: NONGUIDELINE
               Continuous Exponential Model (Decreasing)
               Formula: chei = B + (A-B)*exp(-(m*dose)^g)

Variance Function: power


   The BMD corresponds to a dose that results in a 10% reduction in the
                        response relative to the control
    ------------------------------------------------------------------
                        Summary of Model Fitting Results

      AIC       BIC    logLik
128.17946 133.24610 -61.08973

Coefficients:
      Value  Std.Error
A 7.7267980 0.28009260
m 0.7052234 0.07745722

Correlation:
          A         m
A 1.0000000 0.6121186
m 0.6121186 1.0000000

Approximate 95% confidence intervals

 Coefficients:
      lower      est.    upper
A 7.1800853 7.7267980 8.315139
m 0.5646286 0.7052234 0.880827

 Residual standard error:
   lower     est.    upper
1.134360 1.388028 1.788860

Degrees of freedom: 40 total; 38 residual
    ------------------------------------------------------------------
                              Goodness of Fit
 The chi-squared goodness-of-fit values should be taken as general
indications of fit only.  P-values are likely to be inaccurate to some
degree

Pearson Chi-Square Statistic: 0.1504 with 3 degrees of freedom.  P =
0.985

  dose n chei Expected    sd    Exp.SD    X2 Resid.
1 0.00 8 7.66 7.726798 0.199 1.3985679 -0.135090484
2 0.03 8 7.49 7.565042 0.360 1.3695188 -0.154981141
3 0.11 8 7.30 7.150054 0.426 1.2949706  0.327505621
4 0.30 8 6.25 6.253414 0.427 1.1337783 -0.008516336
```



```
5 1.00 8 3.81 3.817024 1.564 0.6947557 -0.028596565

    ----------------------------------------------------------------
                            BMD Computation

                    BMD = 0.1494:  BMDL = 0.1265

    ----------------------------------------------------------------
                            Potency Measures

A unit dose (1 mg/kg) would result in 100*exp(-Potency)% of background
activity

Potency: 0.7052
se: 0.07746
var=se^2: 0.006
Per cent. of background at unit dose: 49
Per cent. of background at the highest dose: 49
ED50 (95% CI): 0.9829 ( 0.7925 , 1.219 )

ln(Potency) -0.3492
se[log(Potency)]: 0.1098
se[log(Potency)]^2: 0.01206
```

METHYL PARATHION:1-D:BRAIN:M:WHOLE
Fri Jan 04 14:23:32 1980
MRID: 45646501ACPU11Phase2 Guideline: NONGUIDELINE
Continuous Exponential Model (Decreasing)
Formula: chei = B + (A-B)*exp(-(m*dose)^g)

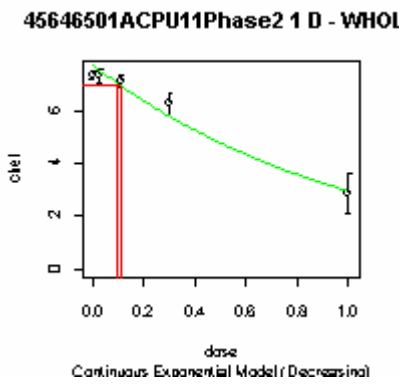
Variance Function: power

The BMD corresponds to a dose that results in a 10% reduction in the response relative to the control

---

Summary of Model Fitting Results

```
      AIC       BIC    logLik
102.81324 107.87987 -48.40662

Coefficients:
     Value  Std.Error
A 7.808377 0.21686653
m 0.963874 0.06213863

Correlation:
          A         m
A 1.0000000 0.5990743
m 0.5990743 1.0000000

Approximate 95% confidence intervals

 Coefficients:
      lower     est.    upper
A 7.3814671 7.808377 8.259976
m 0.8459437 0.963874 1.098245

 Residual standard error:
    lower      est.     upper
0.8454012 1.0344514 1.3331785

Degrees of freedom: 40 total; 38 residual
```



Goodness of Fit

The chi-squared goodness-of-fit values should be taken as general indications of fit only. P-values are likely to be inaccurate to some degree

Pearson Chi-Square Statistic: 4.648 with 3 degrees of freedom. P = 0.199

	dose	n	chei	Expected	sd	Exp.SD	X2 Resid.
1	0.00	8	7.40	7.808377	0.189	1.0752320	-1.0742457
2	0.03	8	7.41	7.585821	0.325	1.0469749	-0.4749847
3	0.11	8	7.18	7.022863	0.284	0.9752001	0.4557539
4	0.30	8	6.33	5.847621	0.514	0.8238399	1.6561161
5	1.00	8	2.89	2.978212	0.903	0.4425588	-0.5637685

BMD Computation

BMD = 0.1093: BMDL = 0.09883

Potency Measures

A unit dose (1 mg/kg) would result in 100*exp(-Potency)% of background activity

Potency: 0.9639
se: 0.06214
var=se^2: 0.003861
Per cent. of background at unit dose: 38
Per cent. of background at the highest dose: 38
ED50 (95% CI): 0.7191 (0.6338 , 0.816)

ln(Potency) -0.03679
se[log(Potency)]: 0.06447
se[log(Potency)]^2: 0.004156

III. Multipathway Graphs for the OP Cumulative Risk Assessment, 2006 Update

A. Region A

Figure III.A-1 Infants Region A Surface Water (No oxon) DDVP, 21-day; MOEs at the 95th percentile

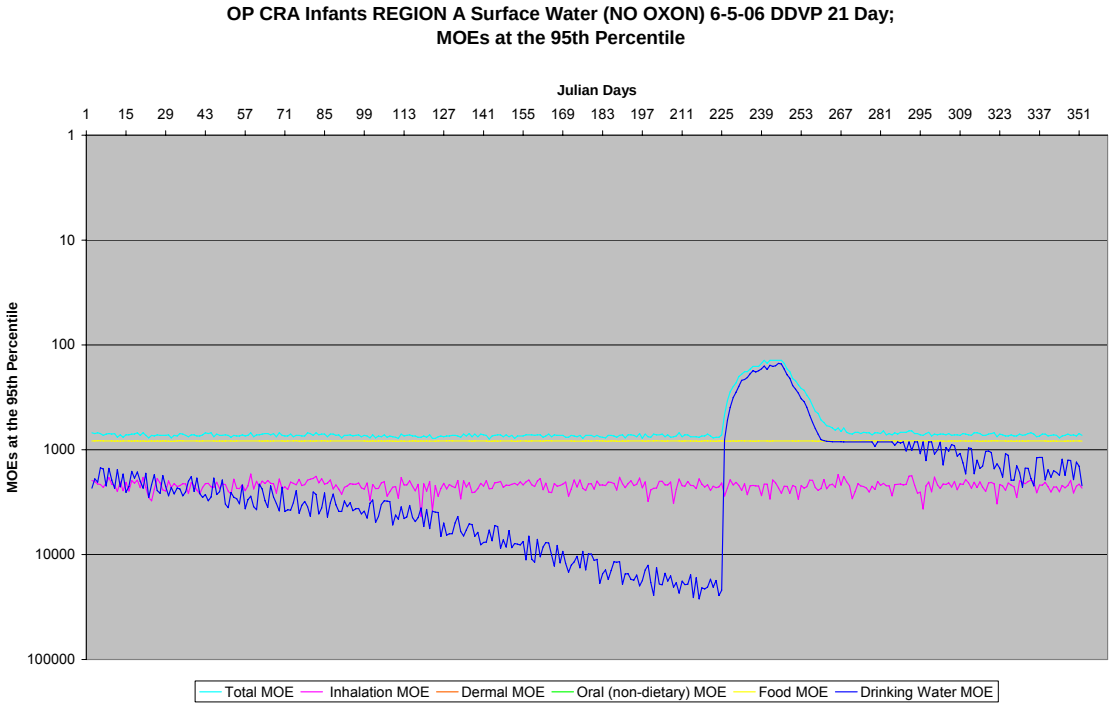


Figure III.A 2

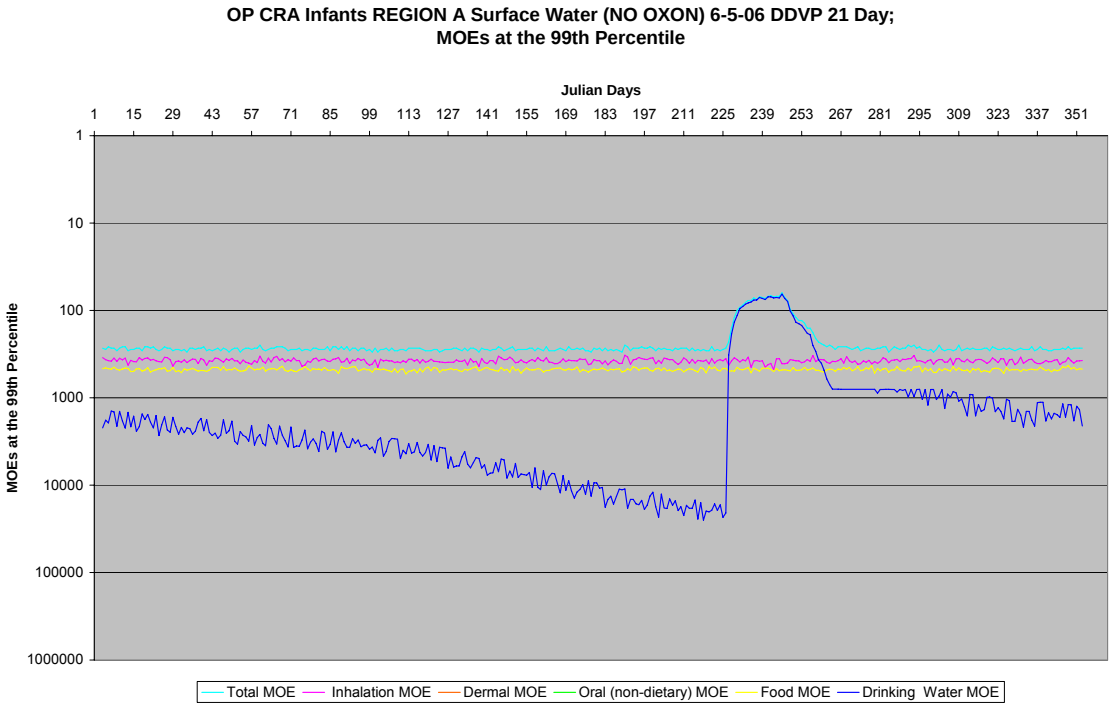


Figure III.A 3

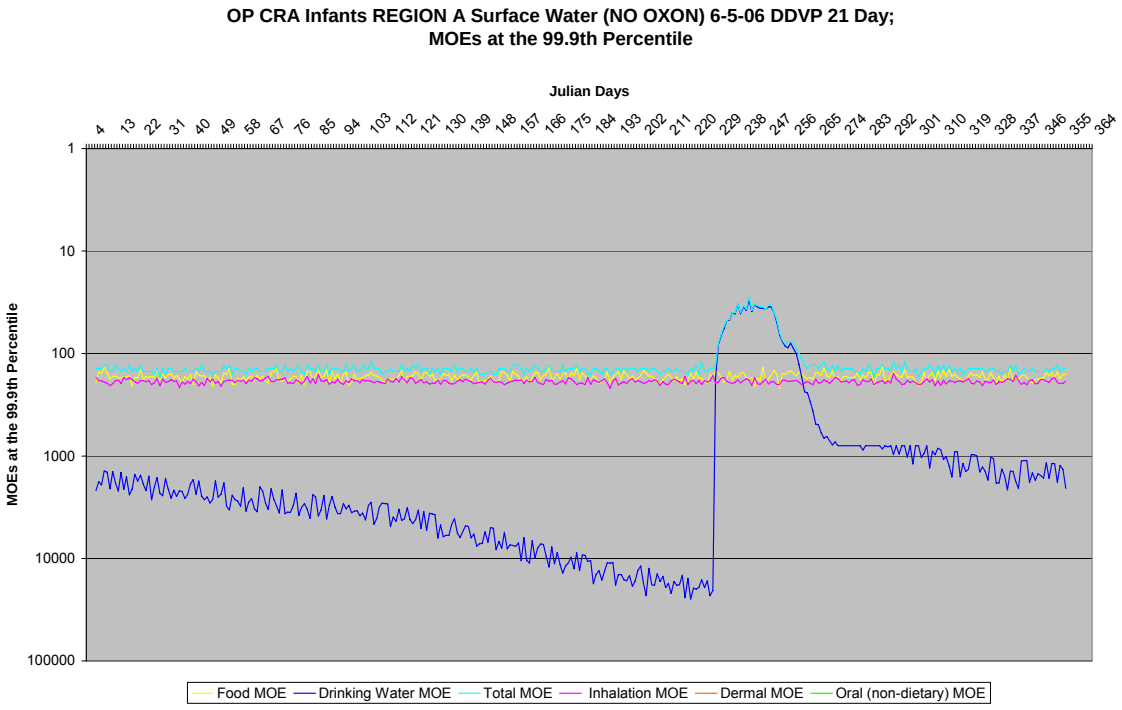


Figure III.A 4

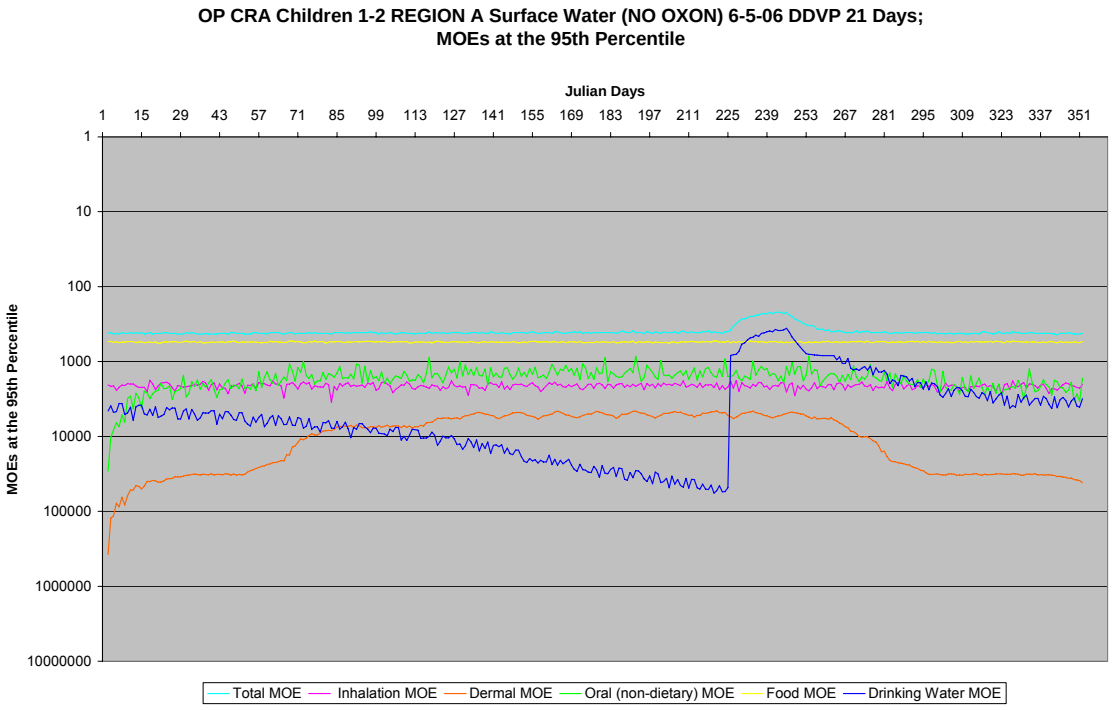


Figure III.A 5

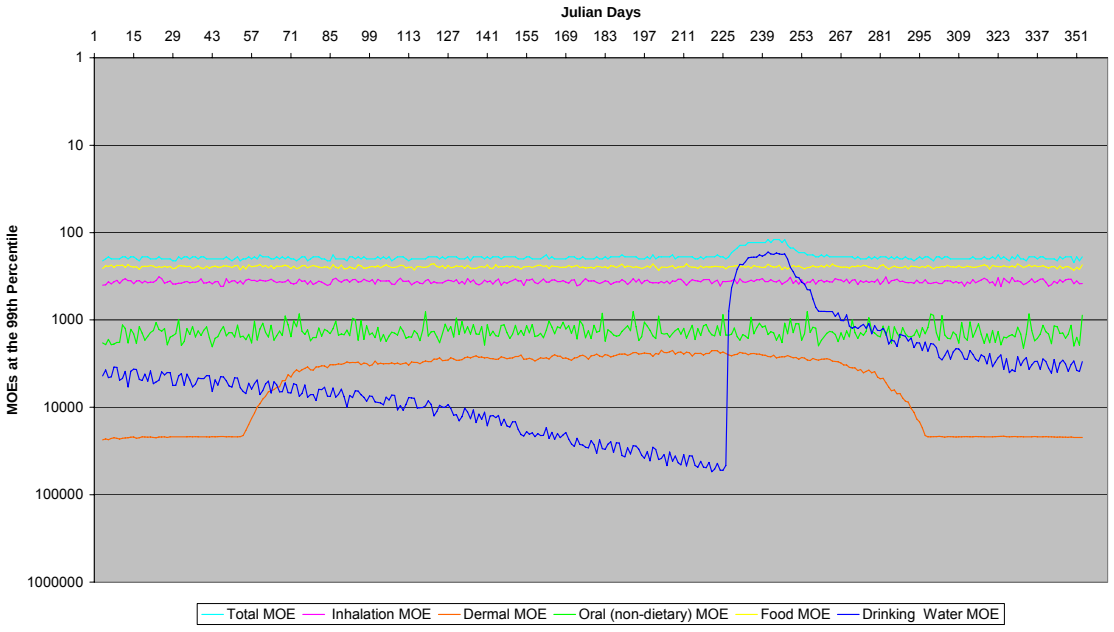


Figure III.A 6

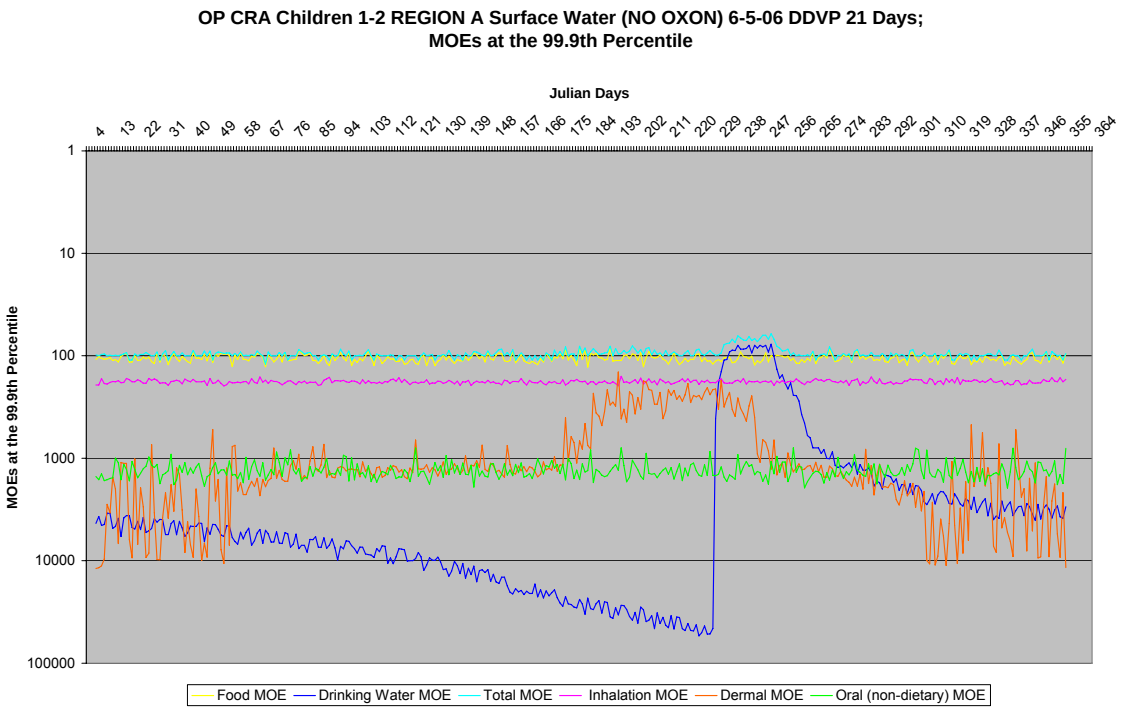


Figure III.A 7

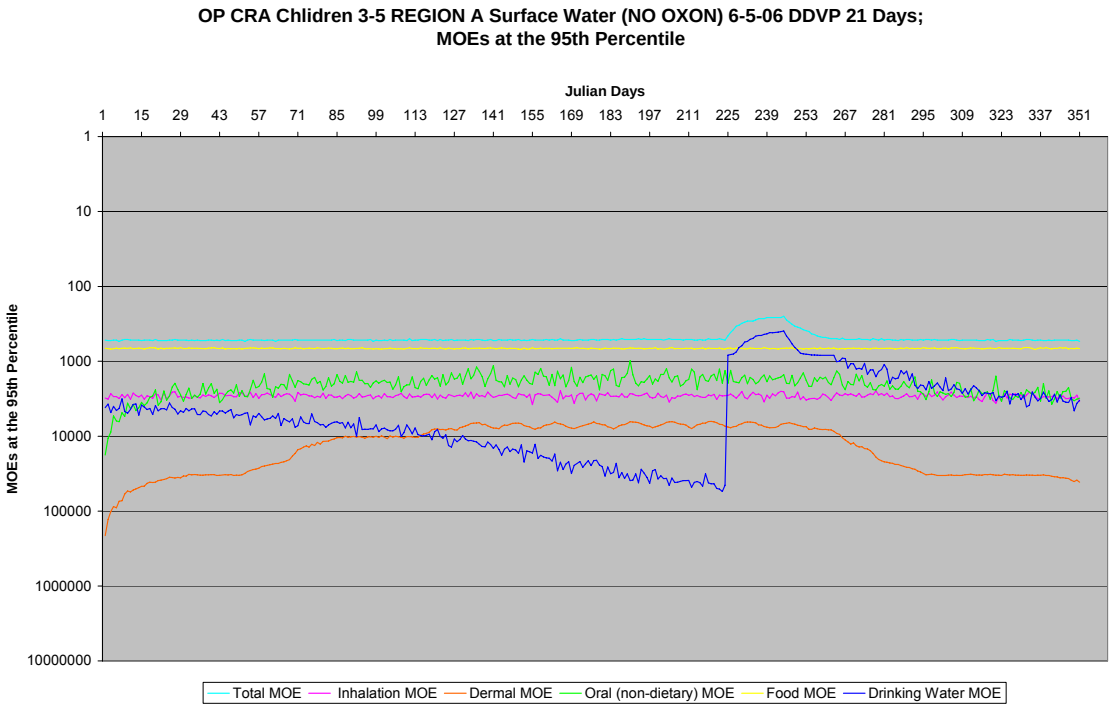


Figure III.A 8

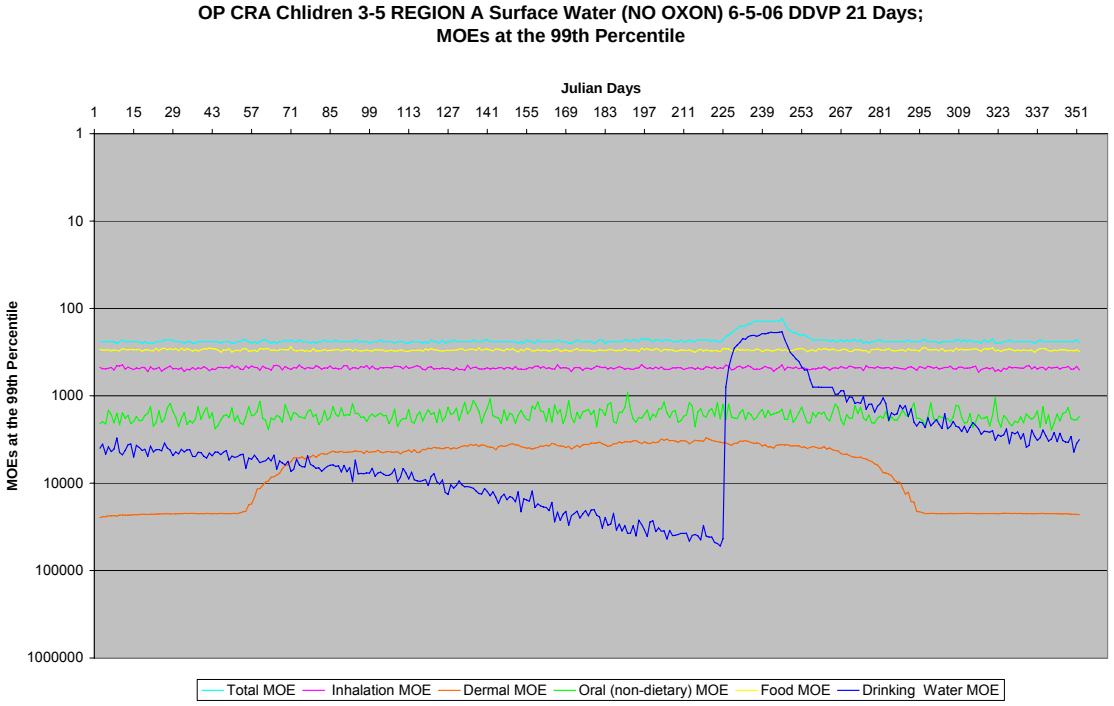


Figure III.A 9

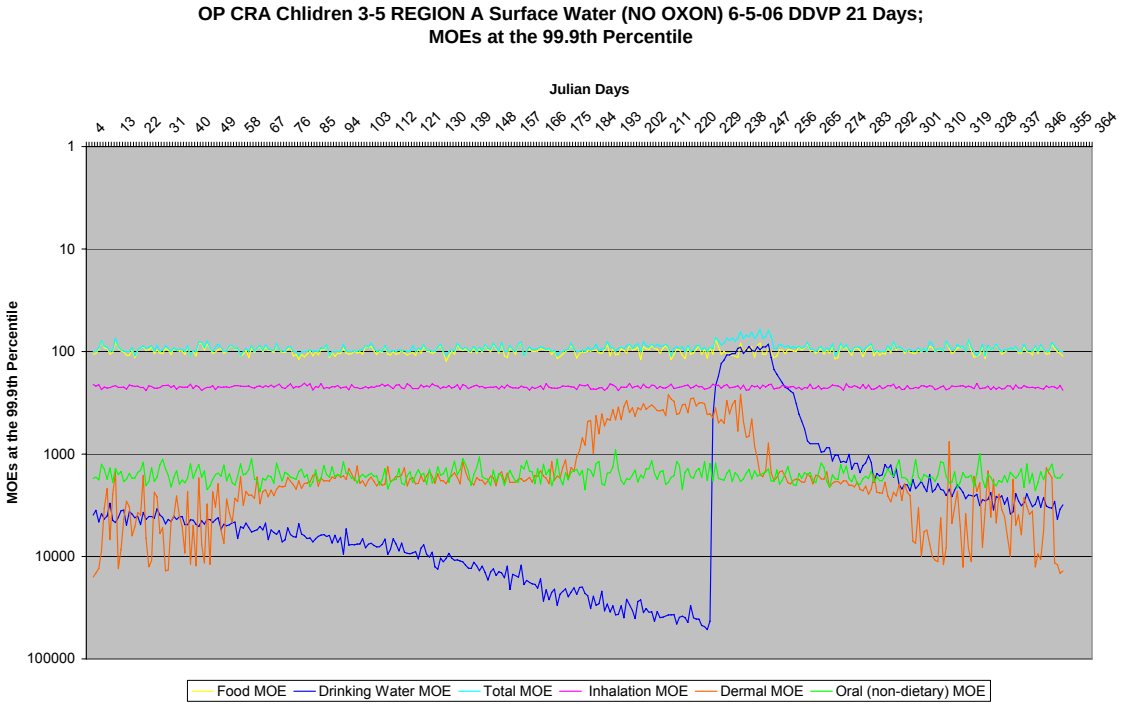


Figure III.A 10

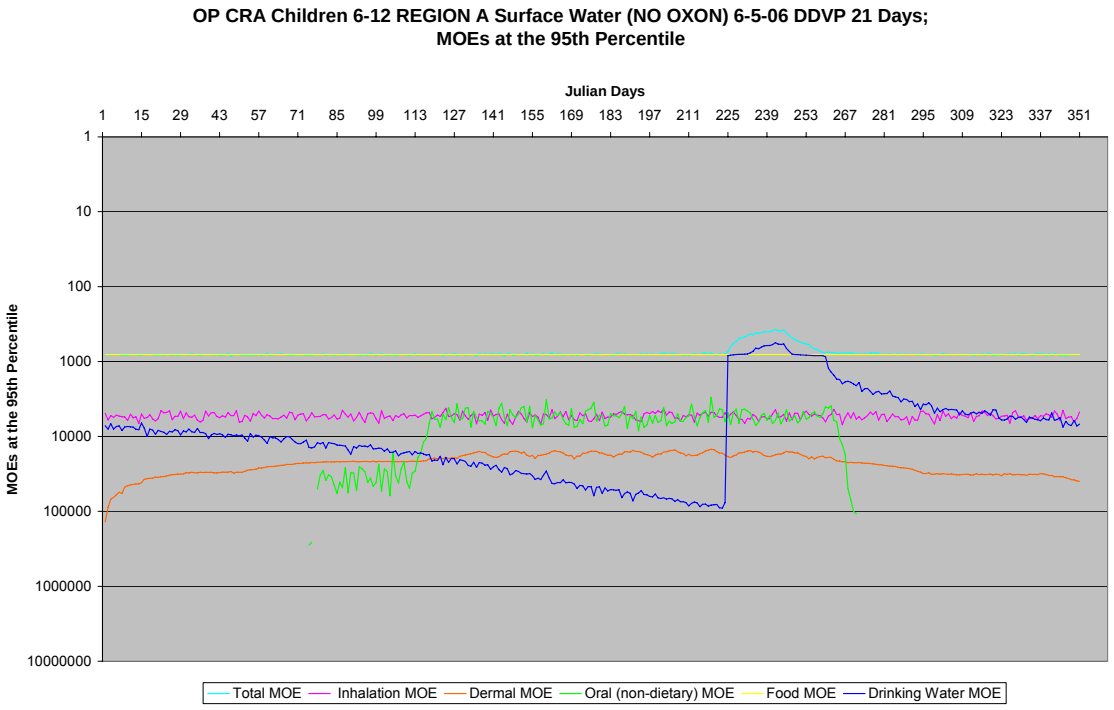


Figure III.A 11

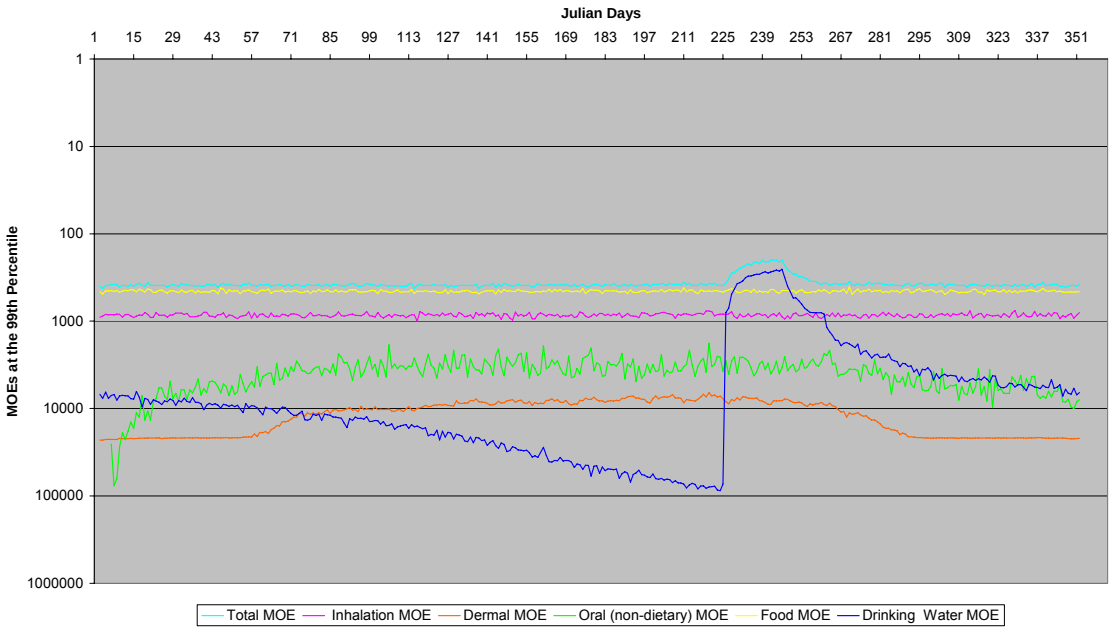


Figure III.A 12

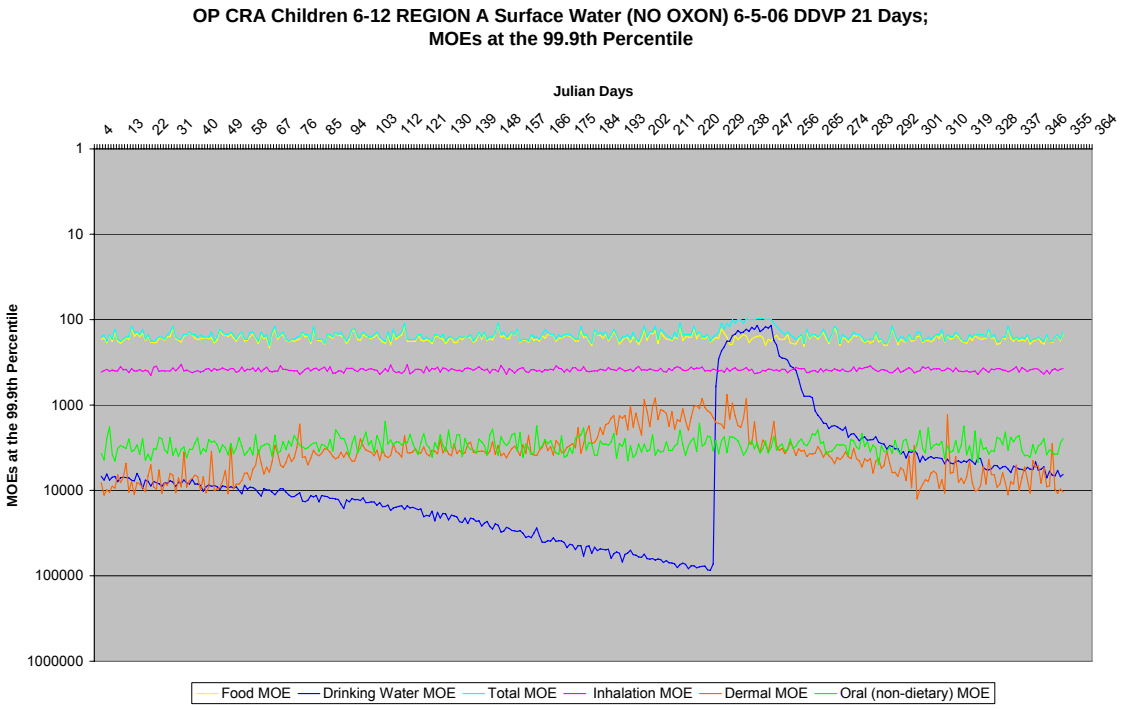


Figure III.A 13

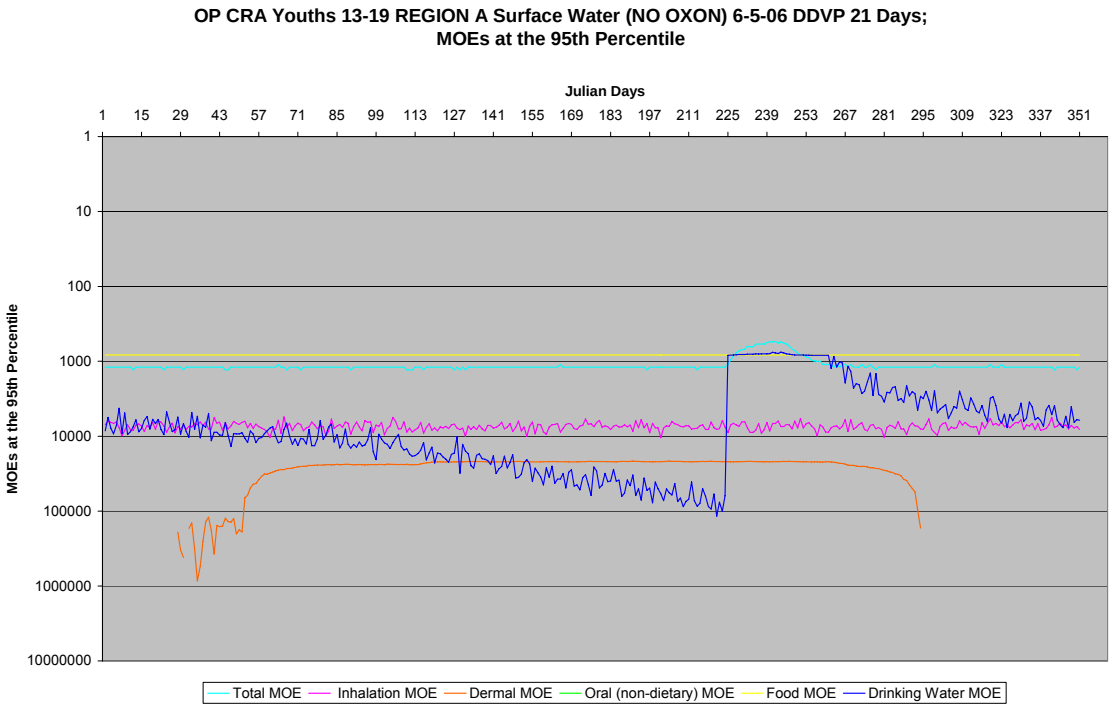


Figure III.A 14

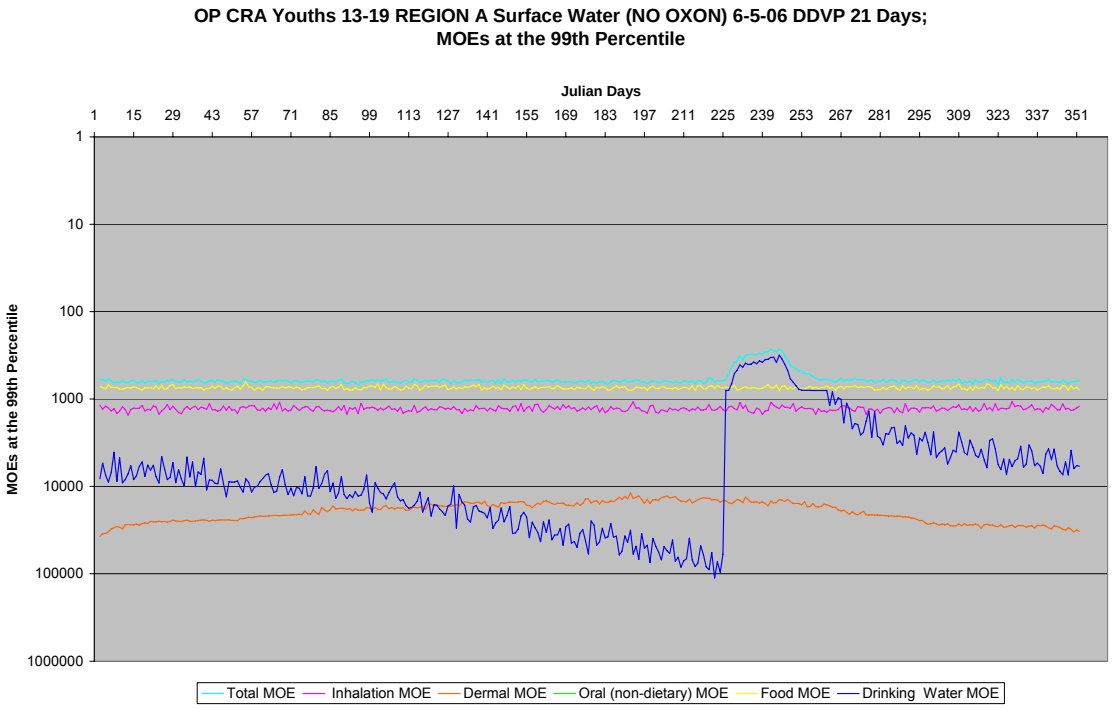
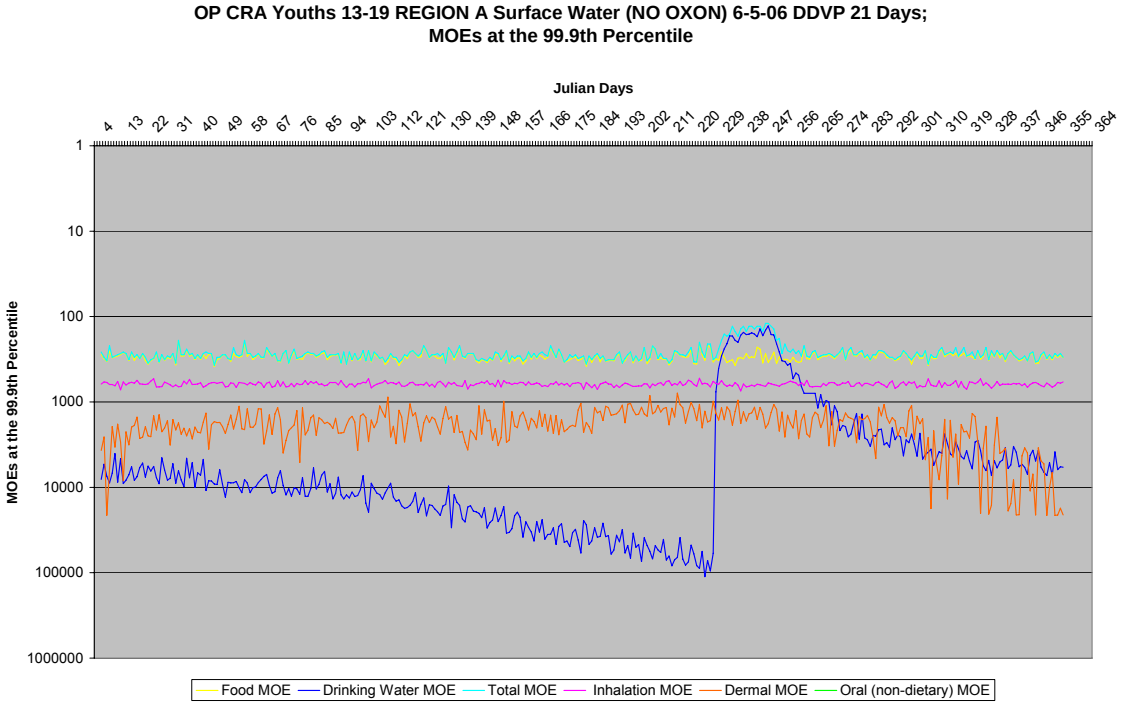


Figure III.A 15



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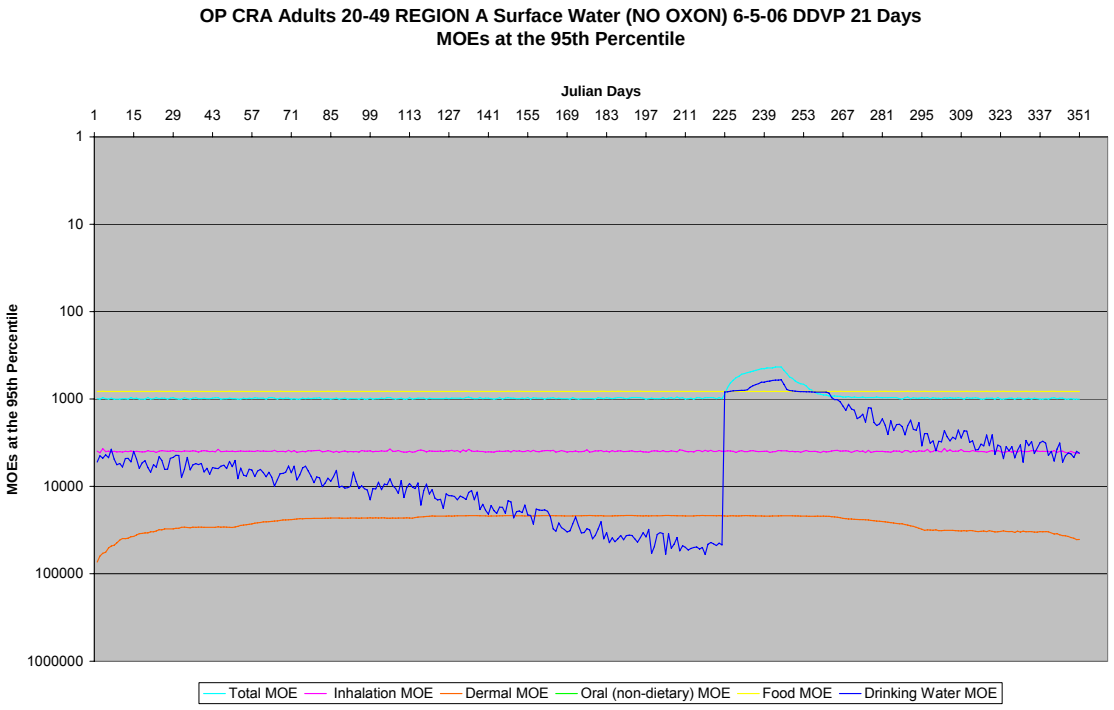

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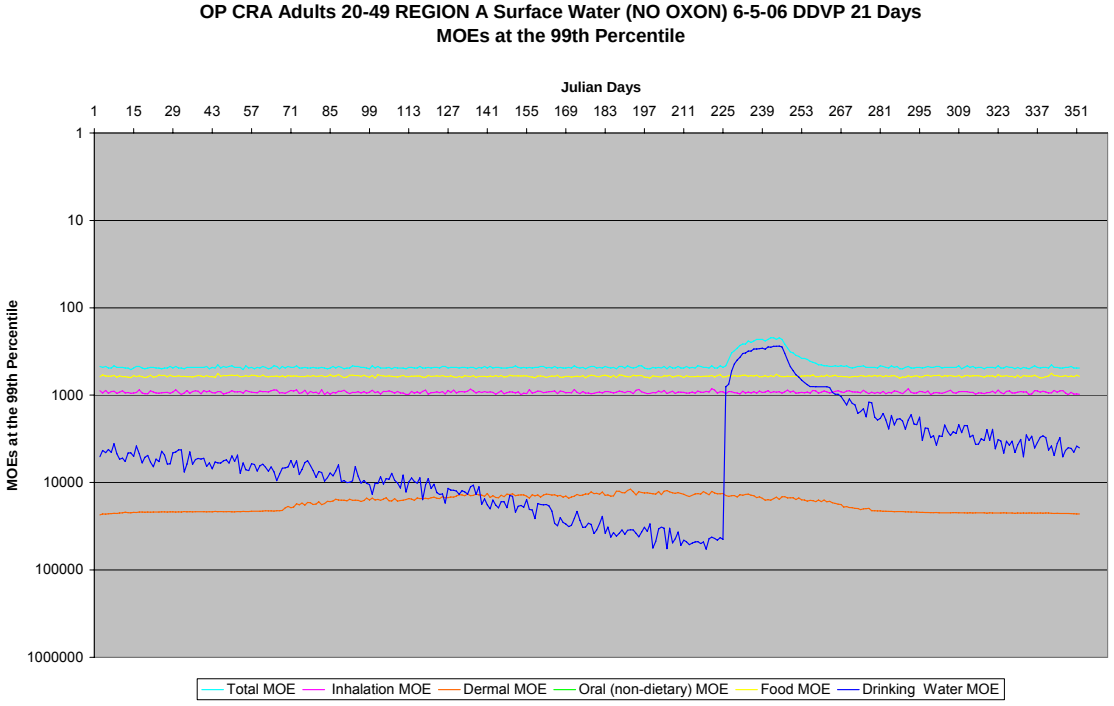

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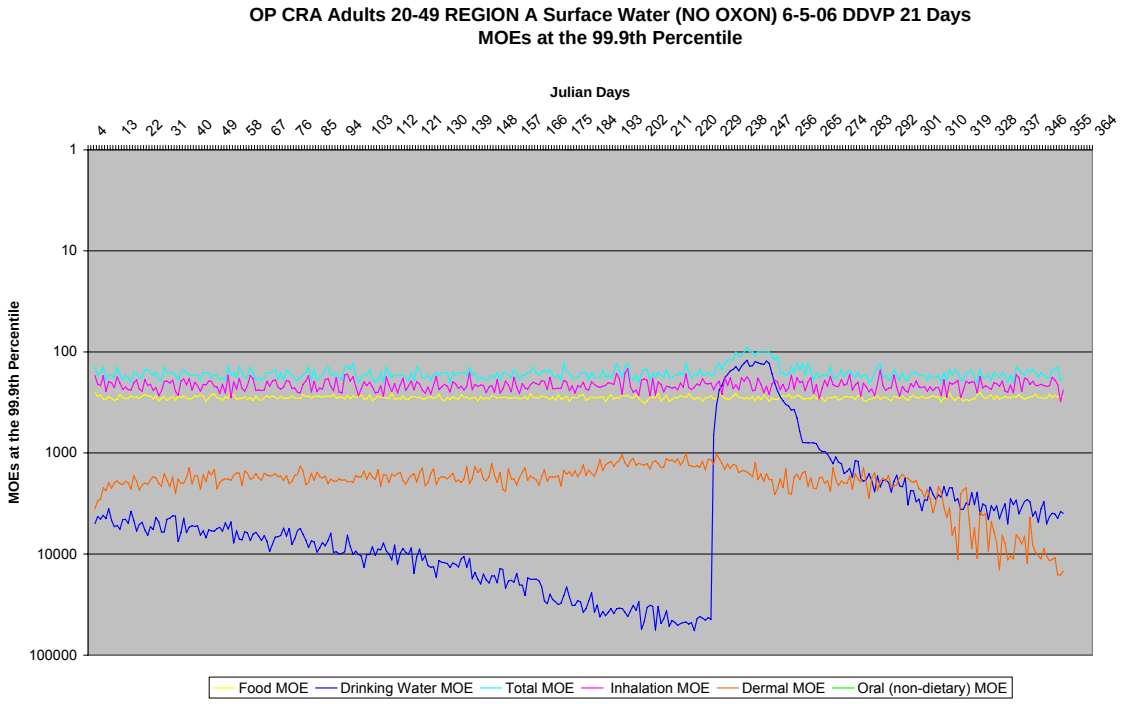


Figure III.A 19

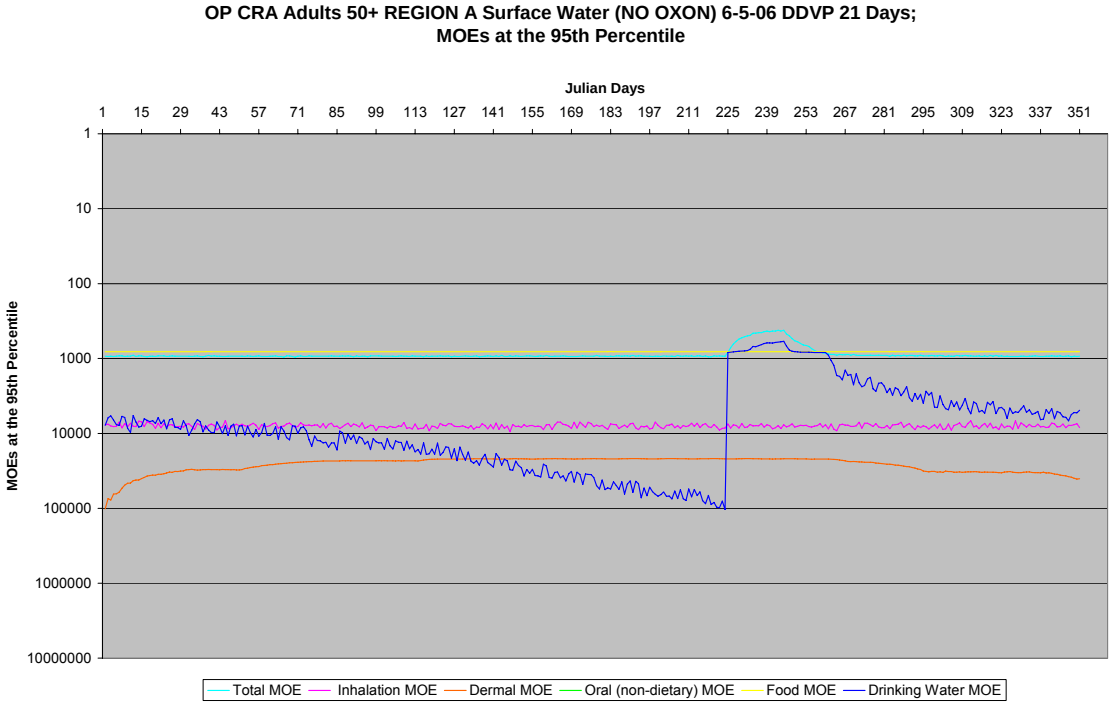


Figure III.A 20

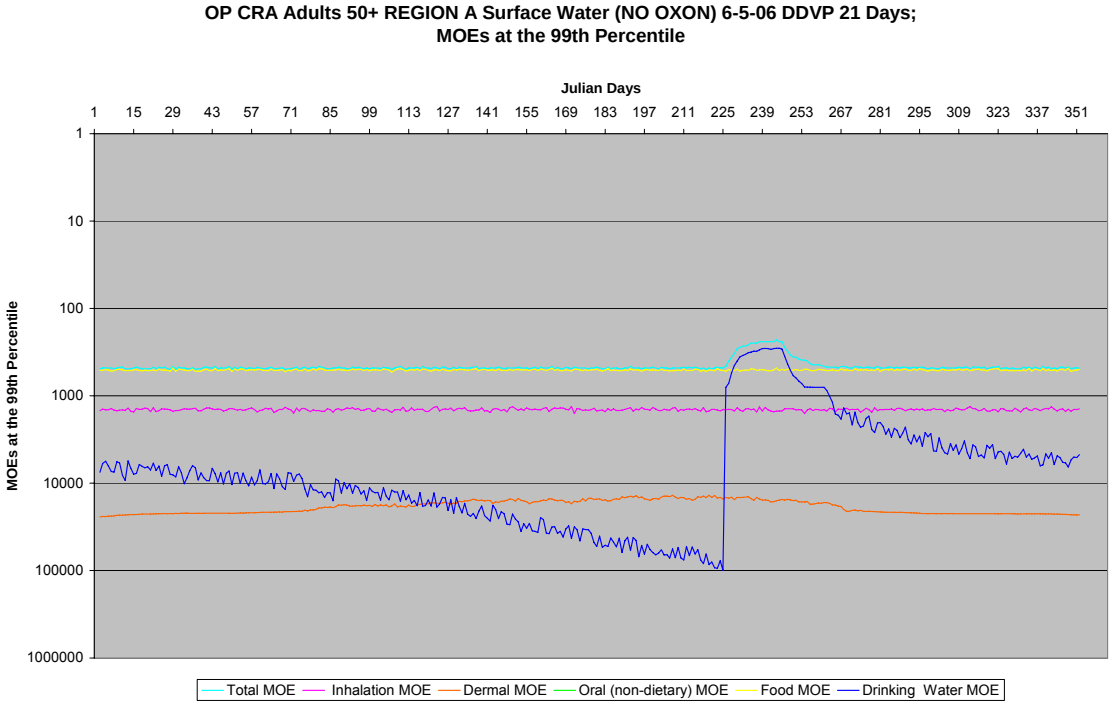
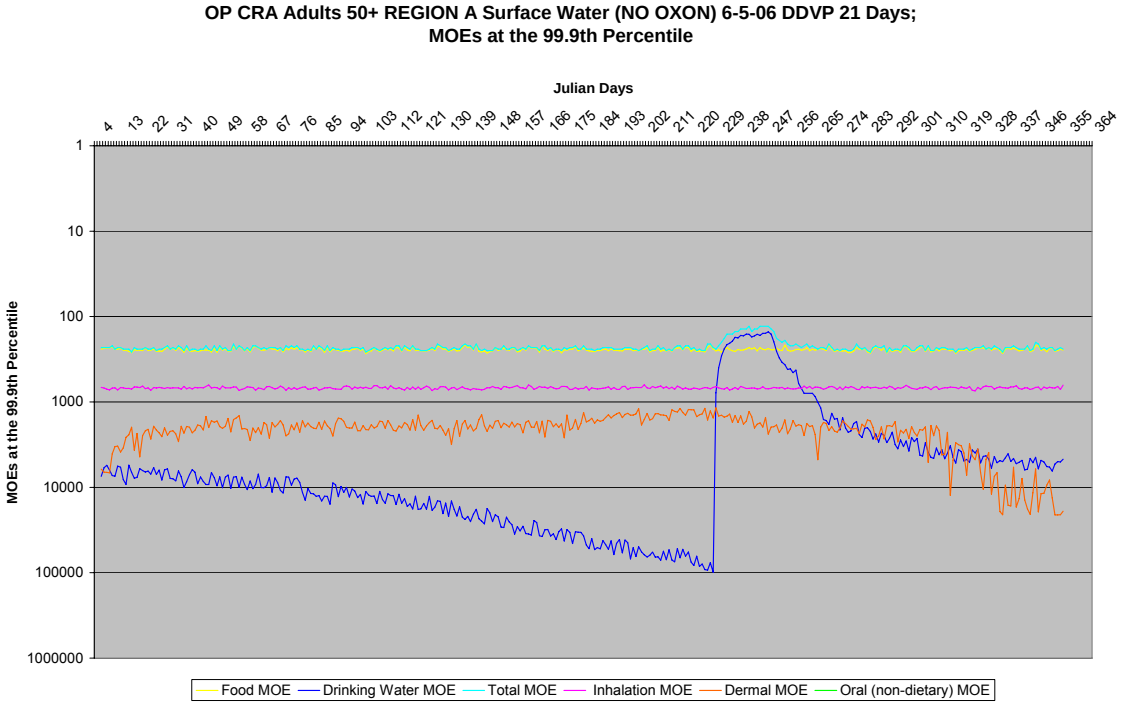


Figure III.A 21



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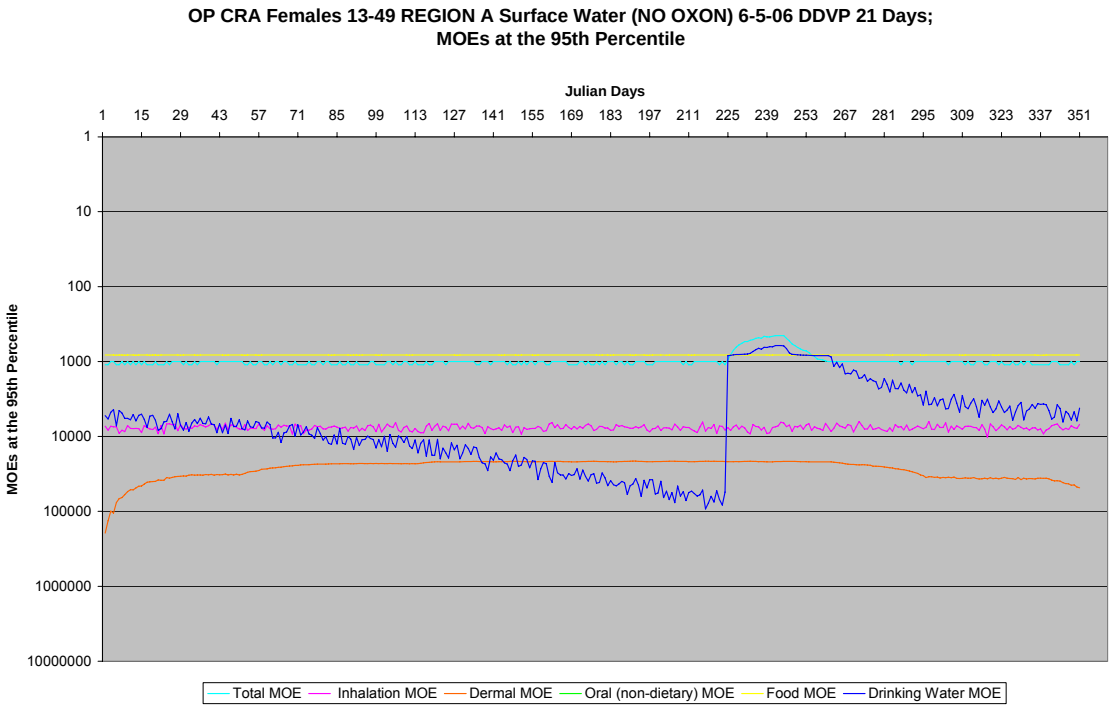

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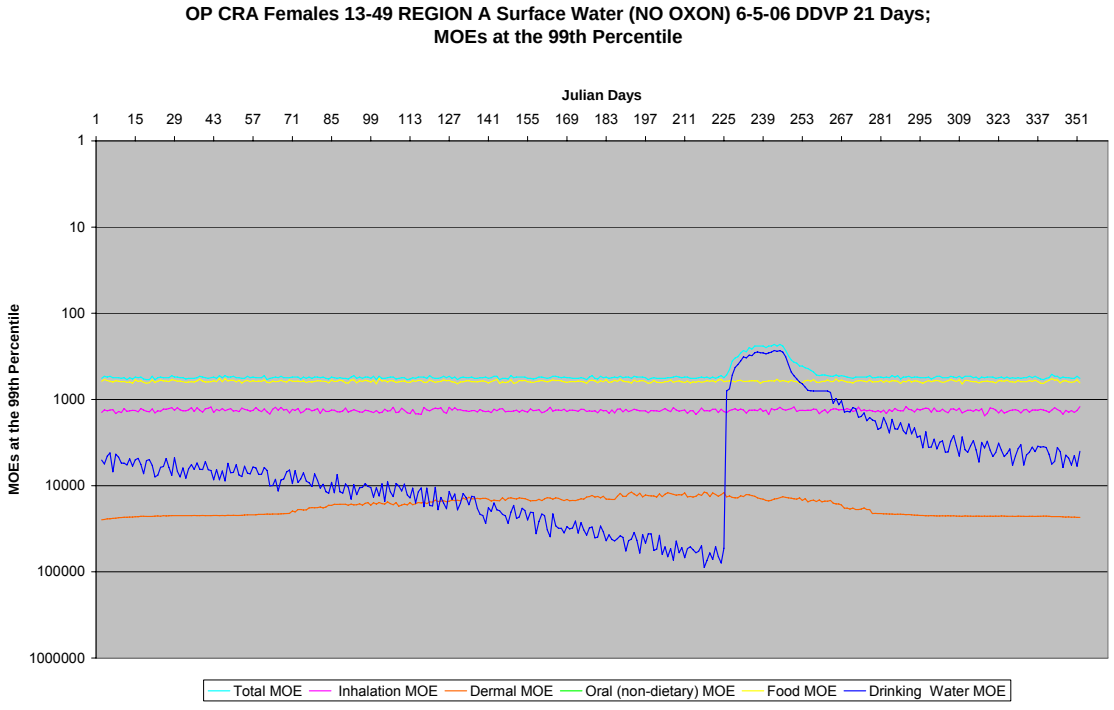

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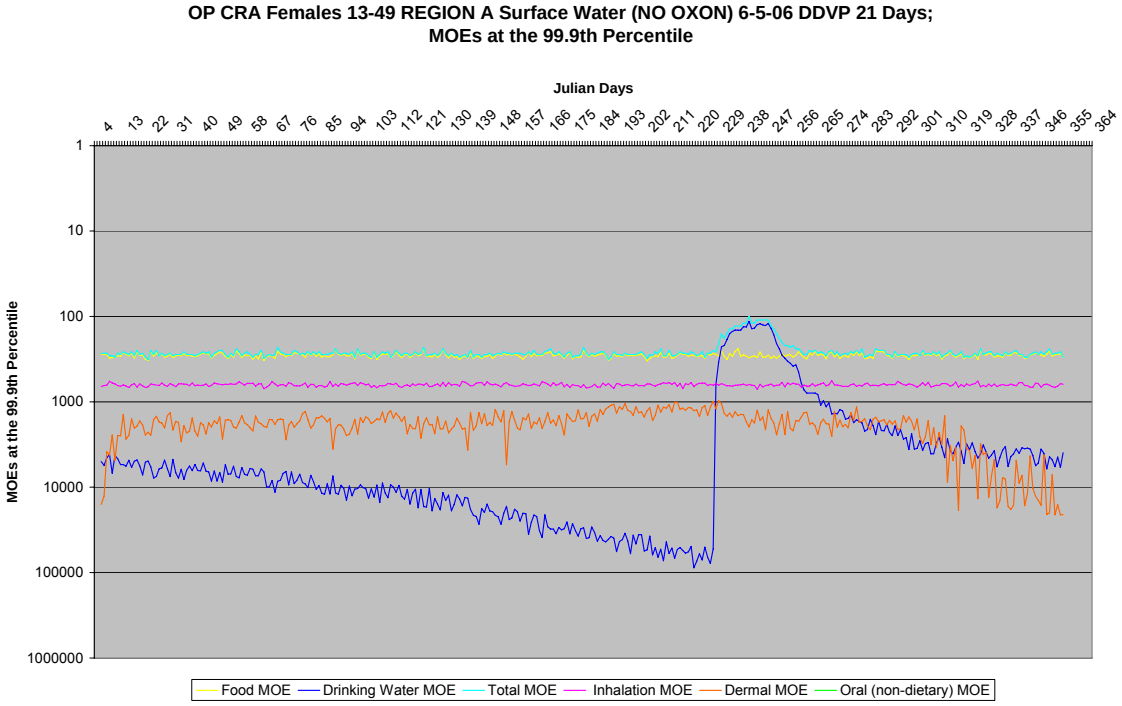

B. Region C 1x

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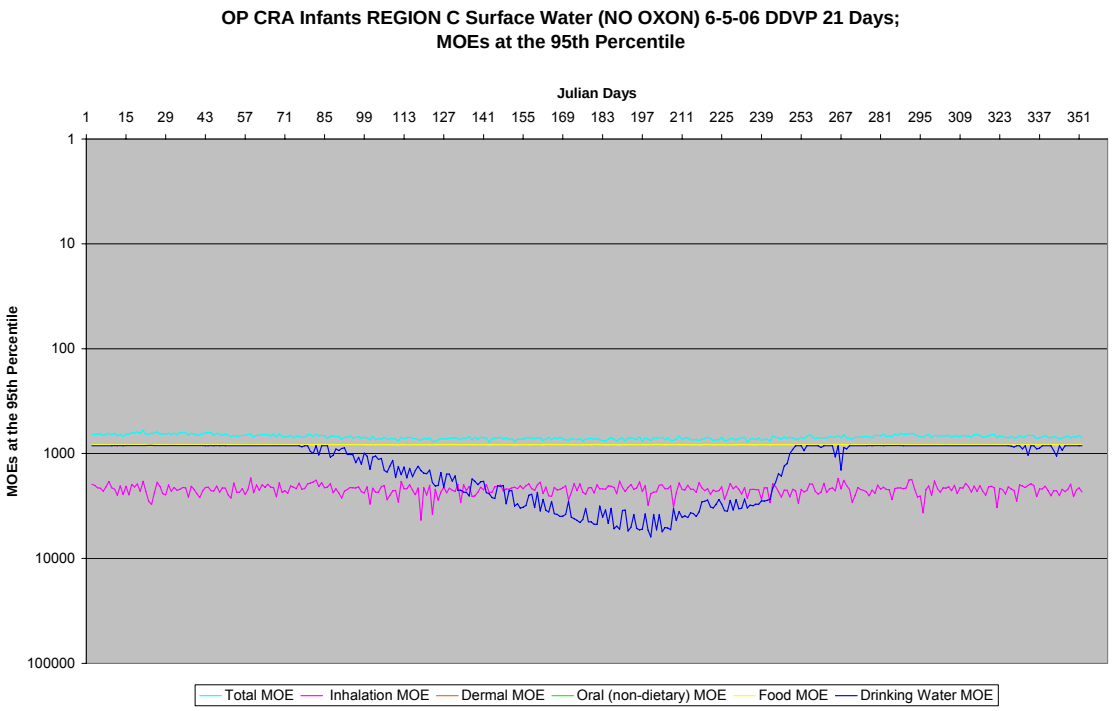
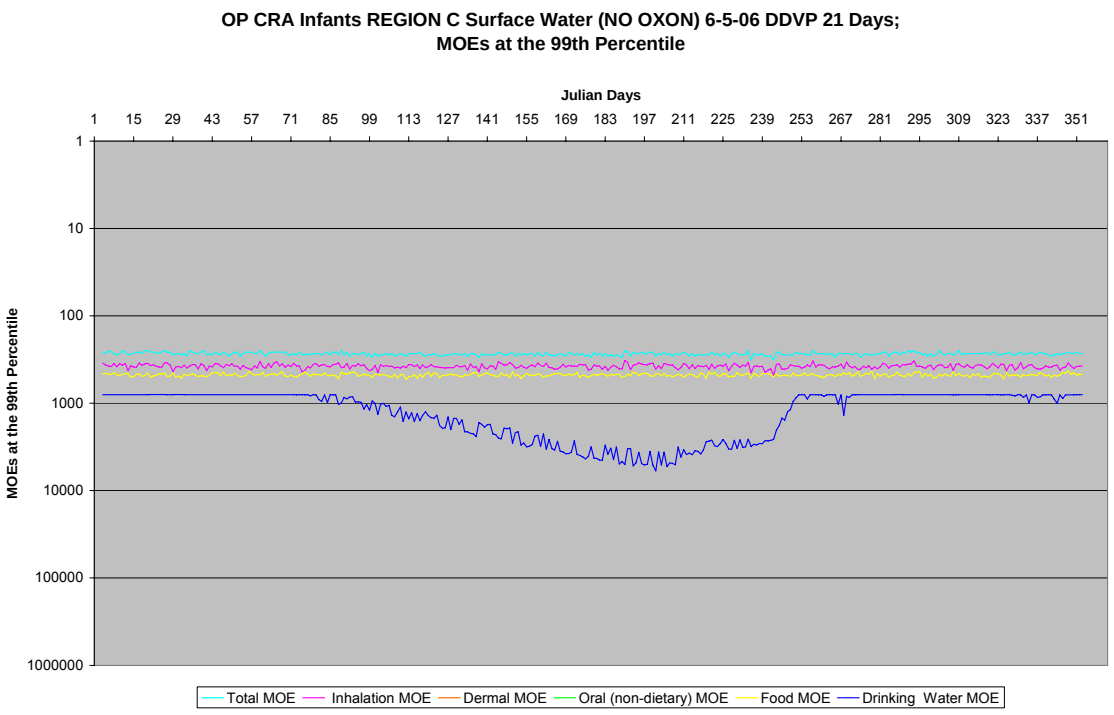


Figure III.B 2



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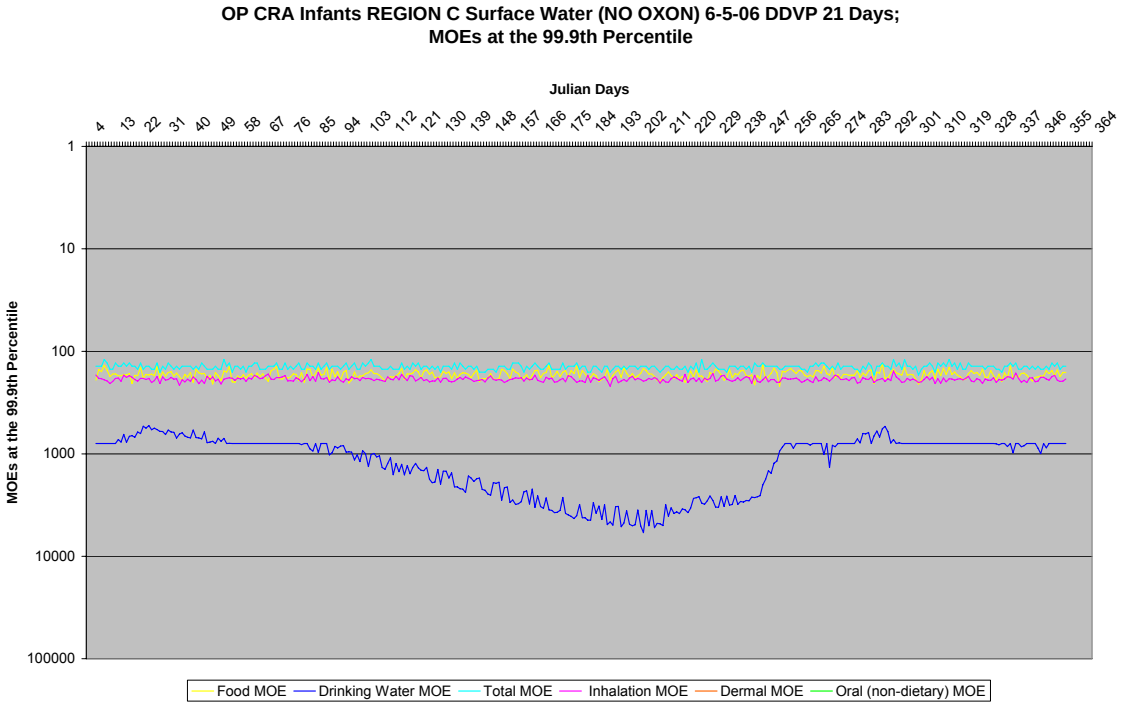

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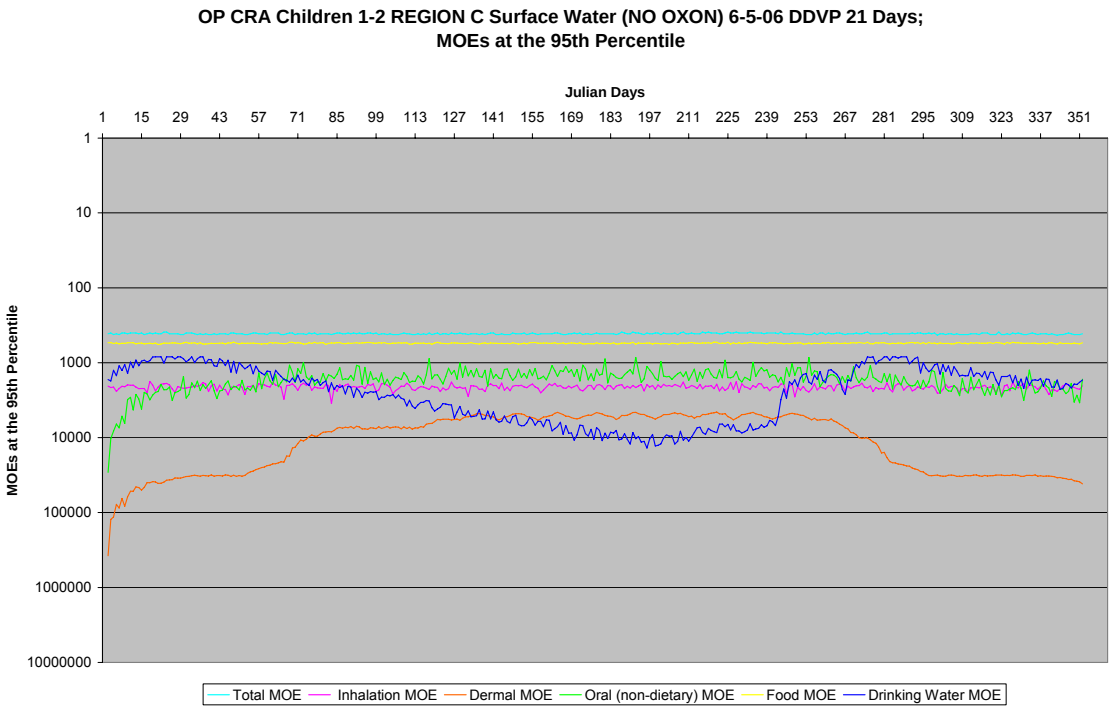

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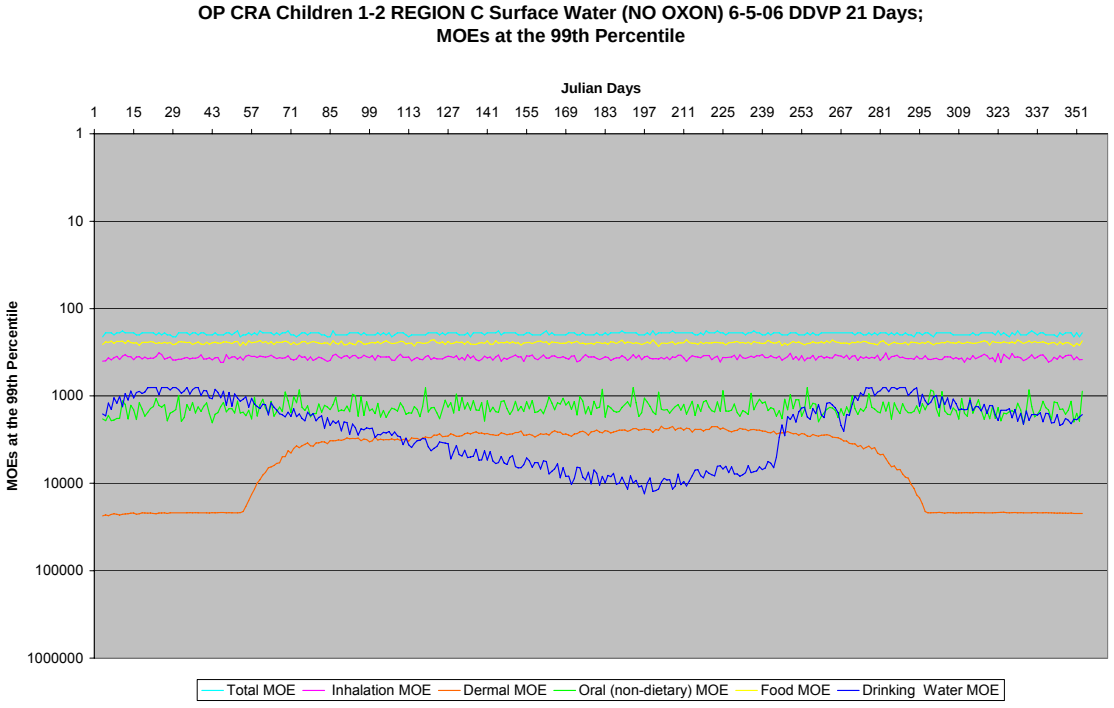
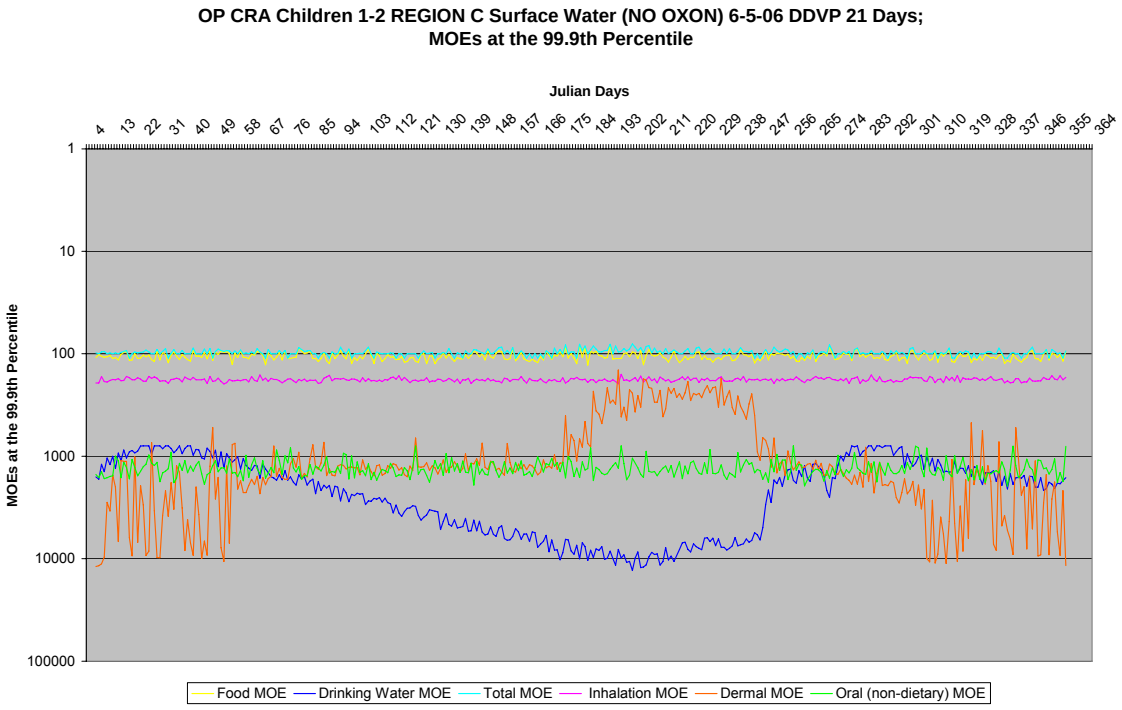


Figure III.B 6



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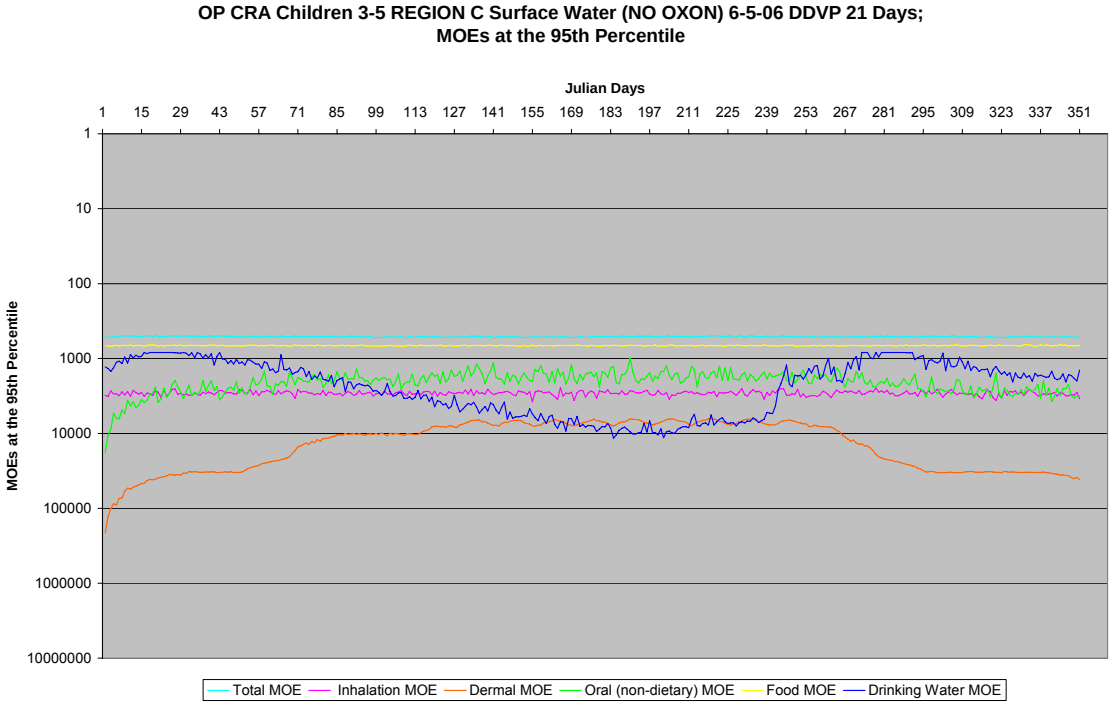
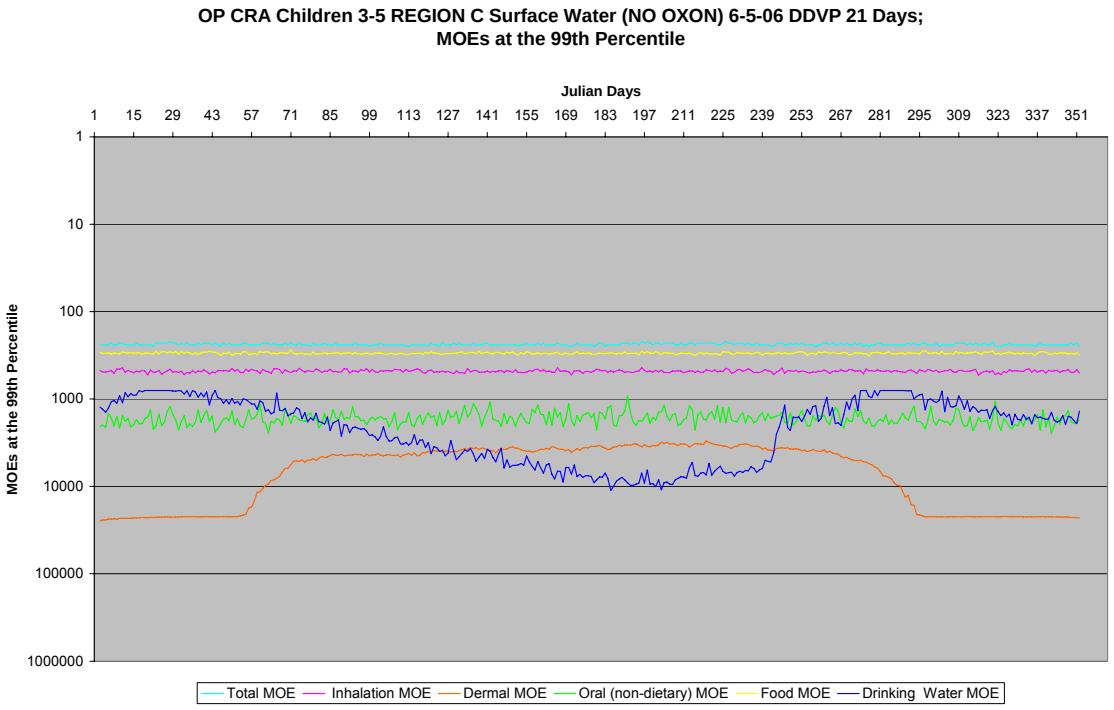


Figure III.B 8



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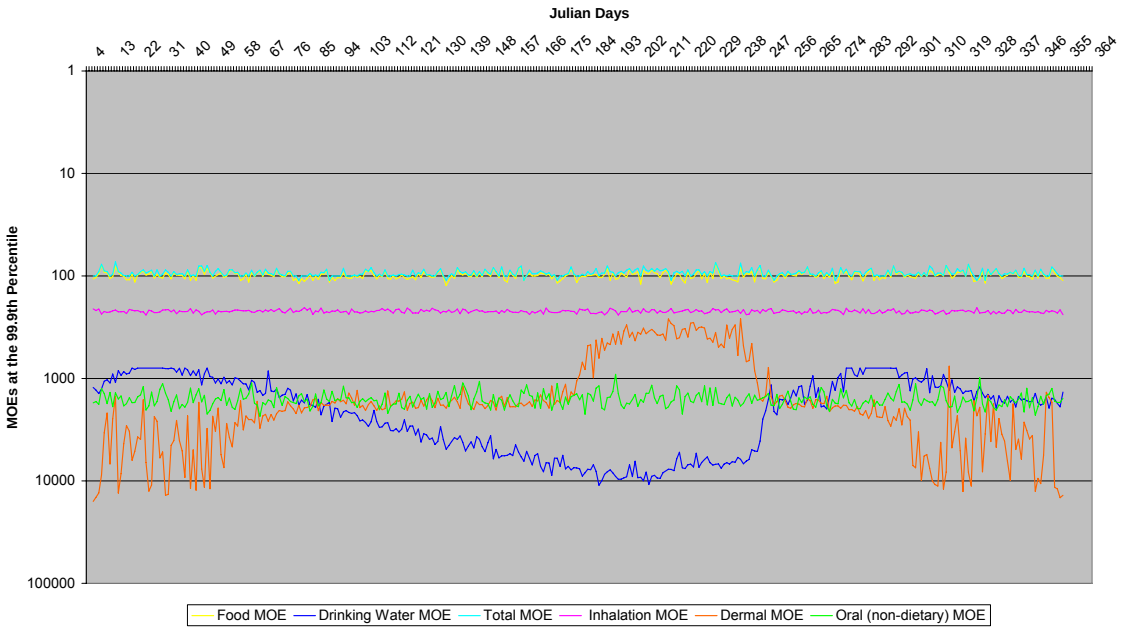
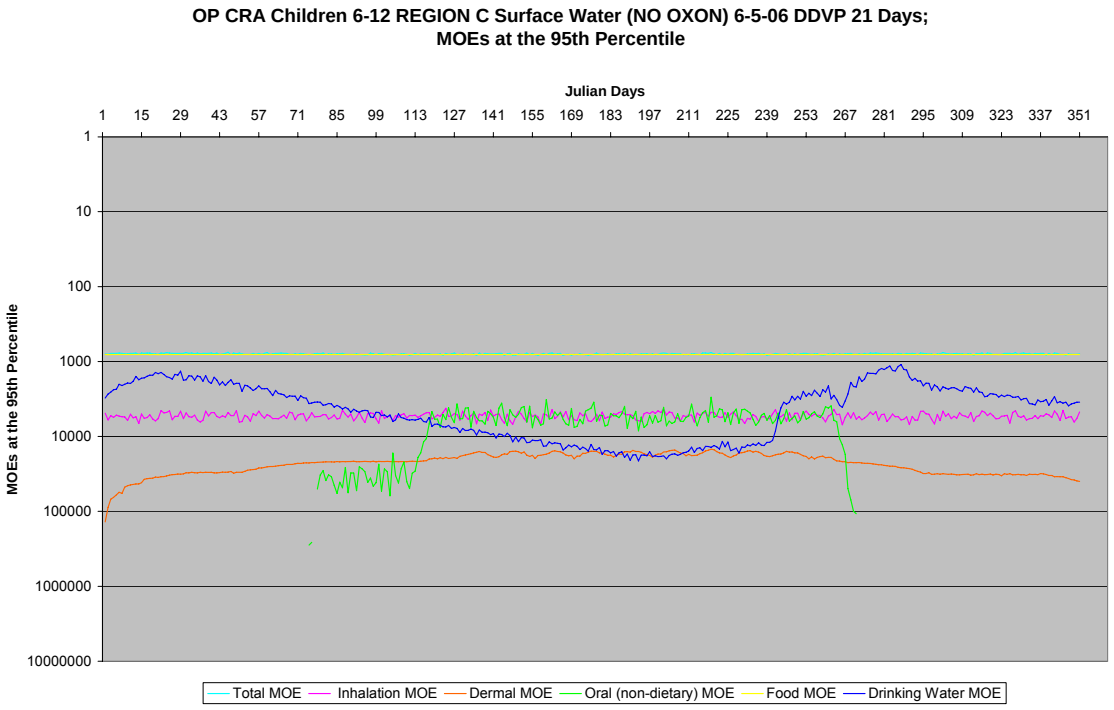


Figure III.B 10



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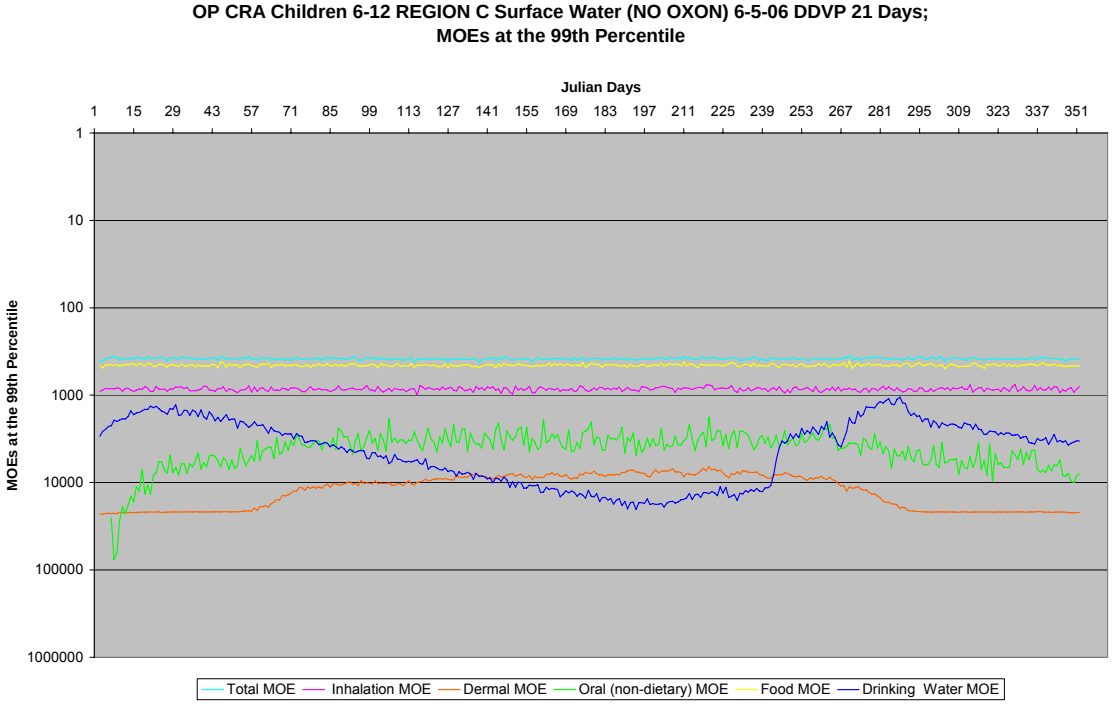


Figure III.B 12

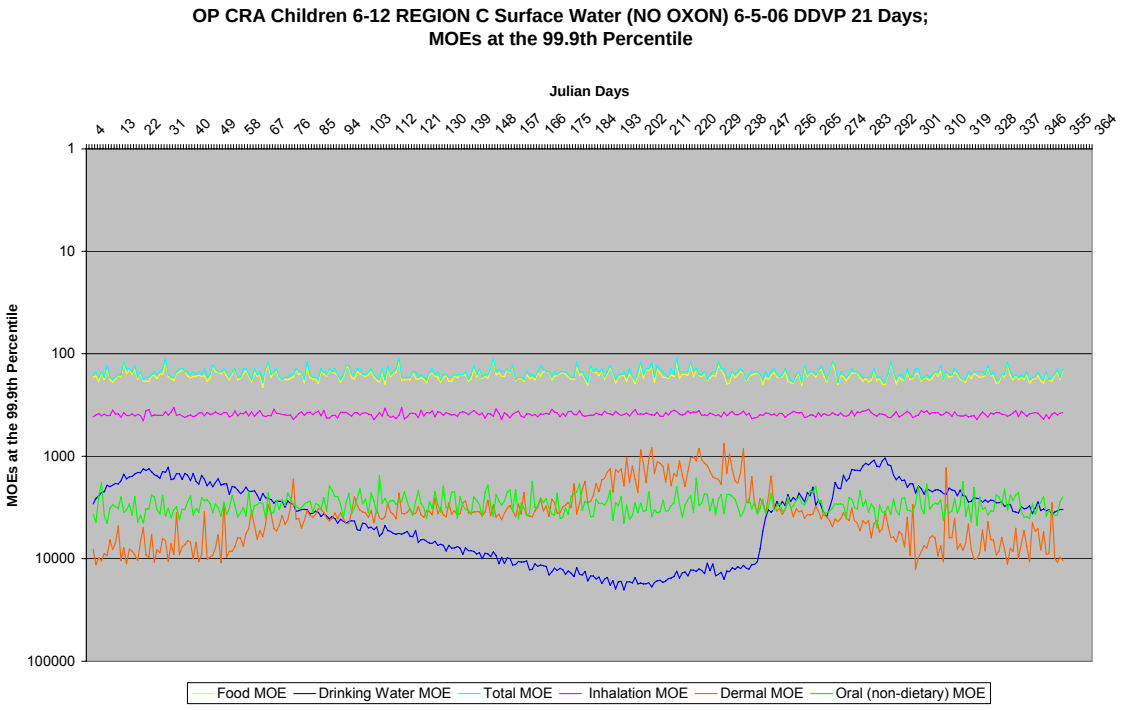


Figure III.B 13

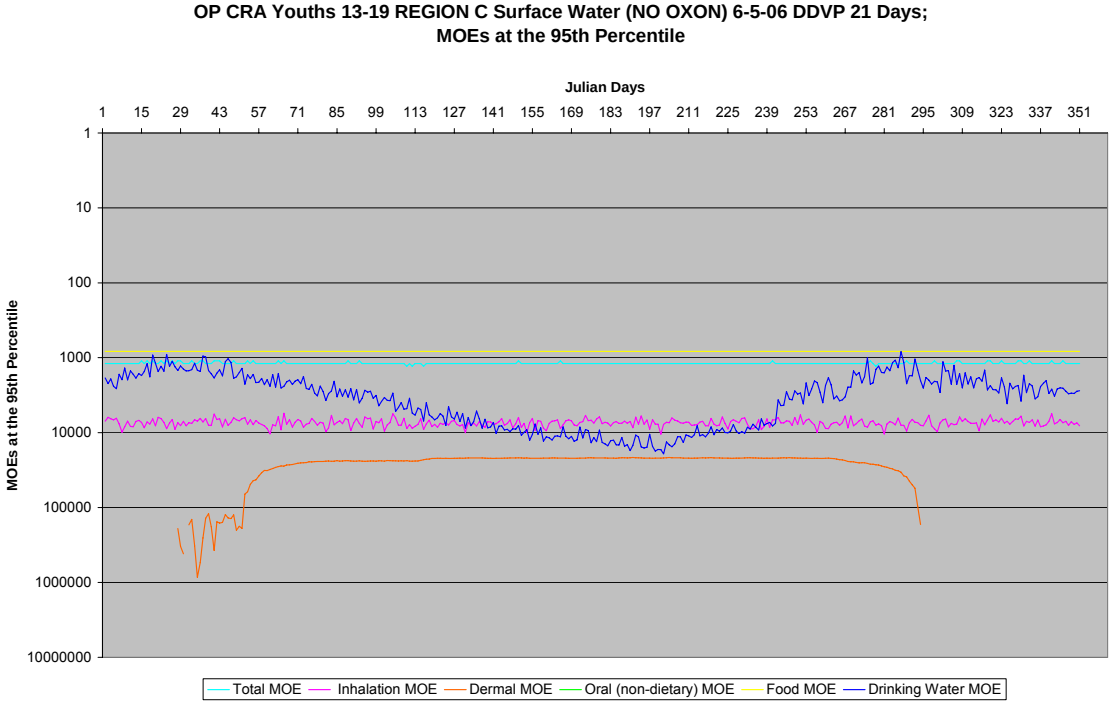


Figure III.B 14

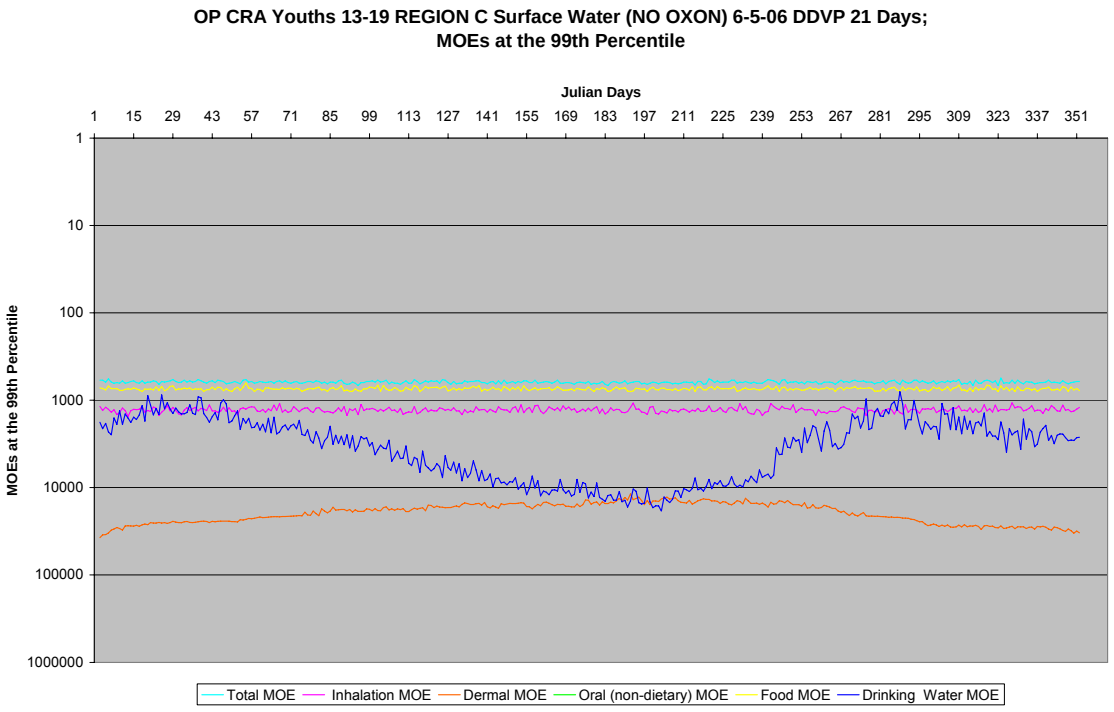
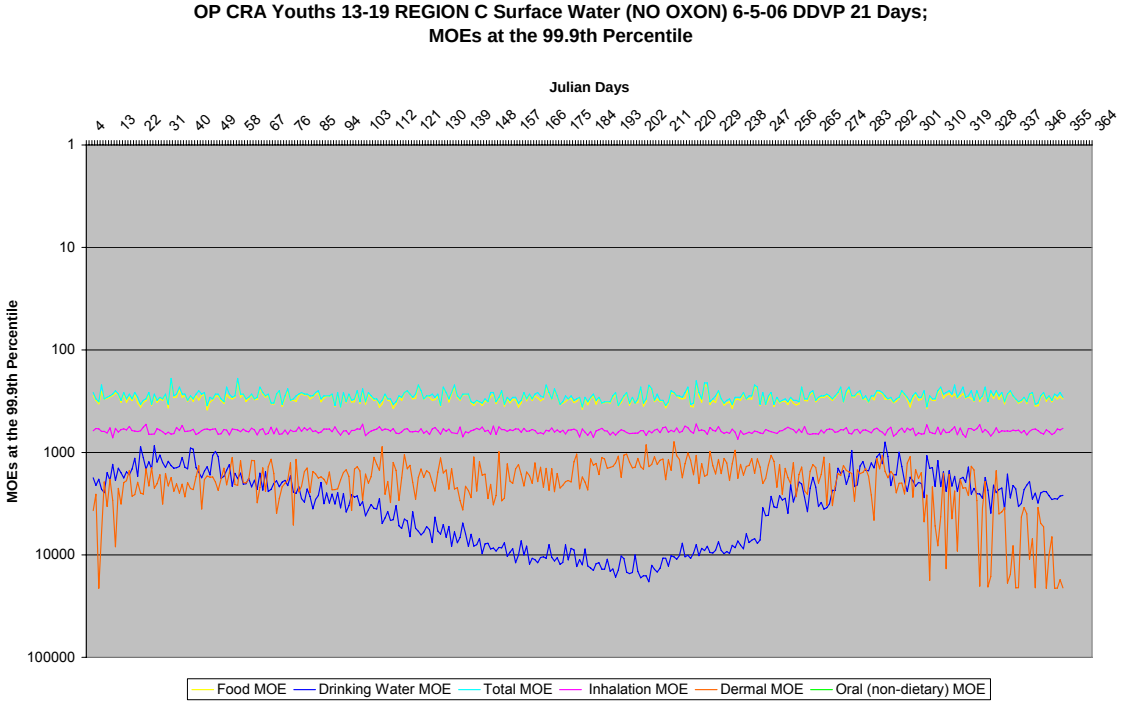


Figure III.B 15



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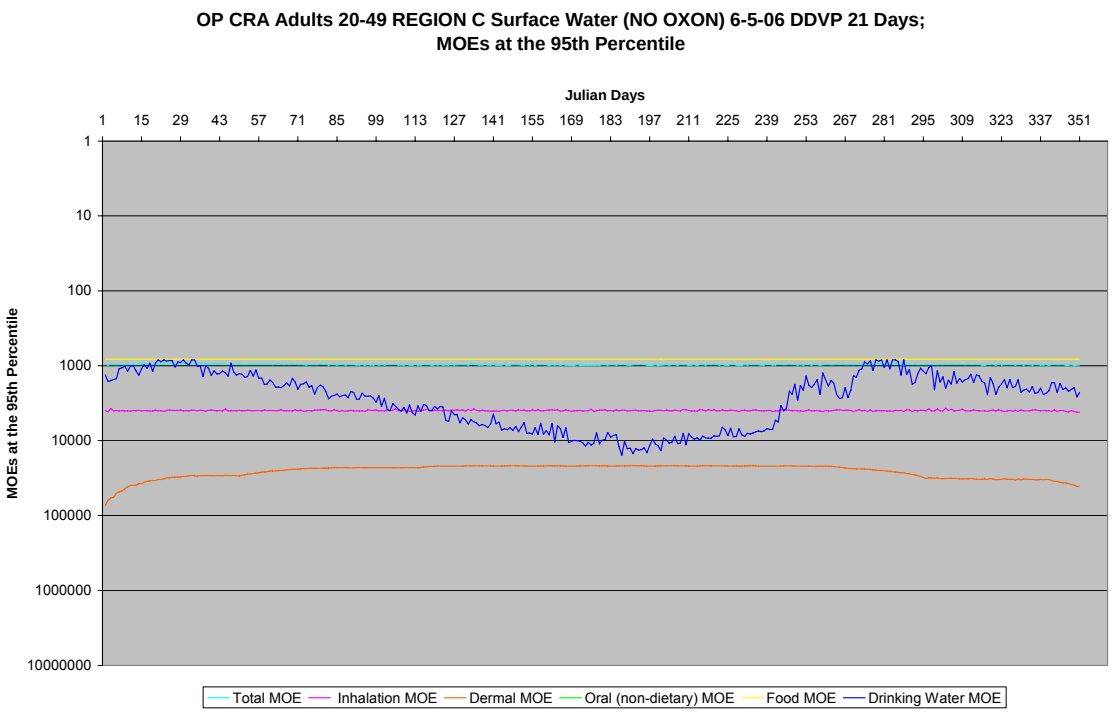


Figure III.B 17

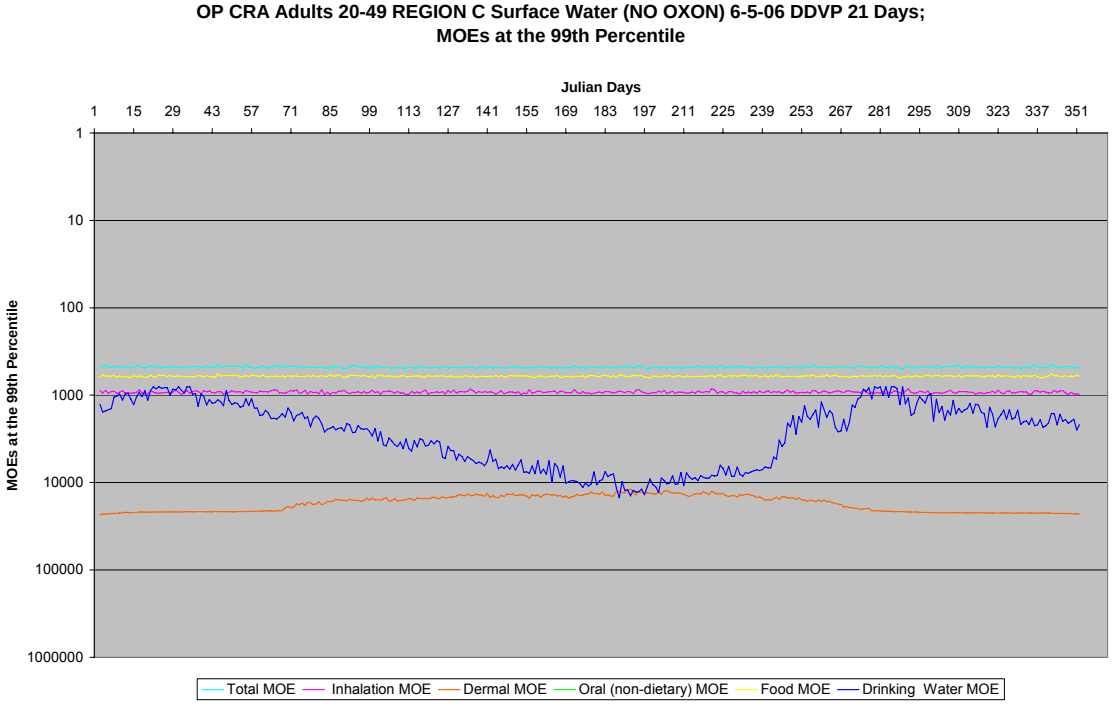


Figure III.B 18

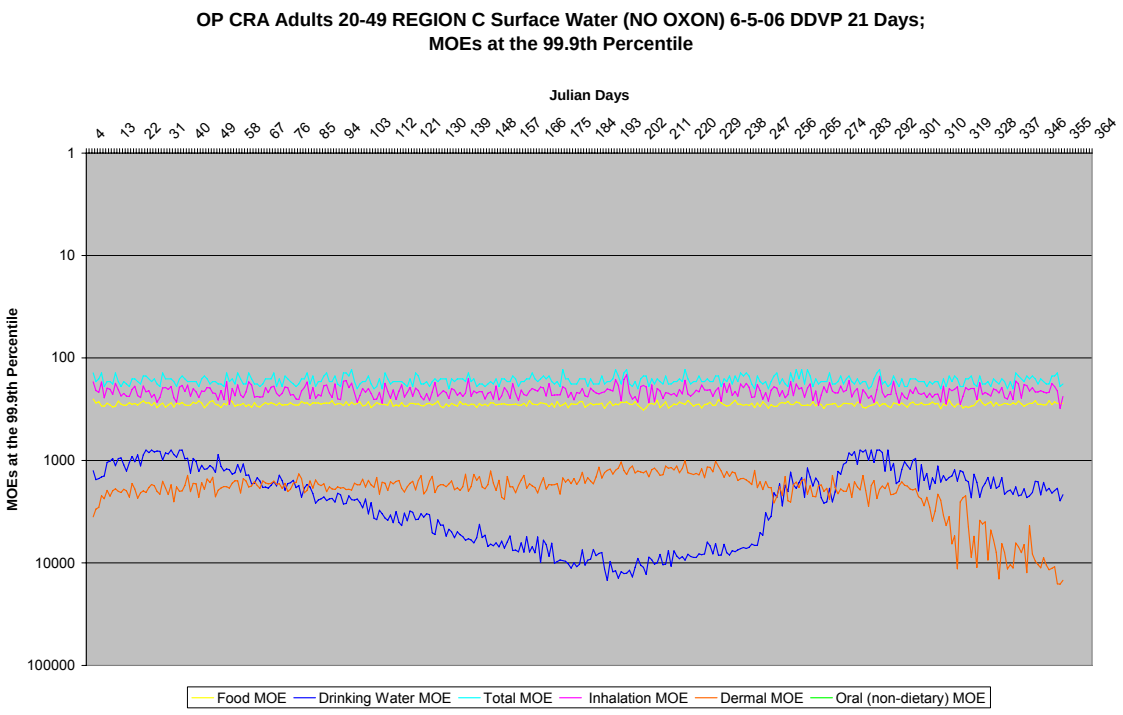


Figure III.B 19

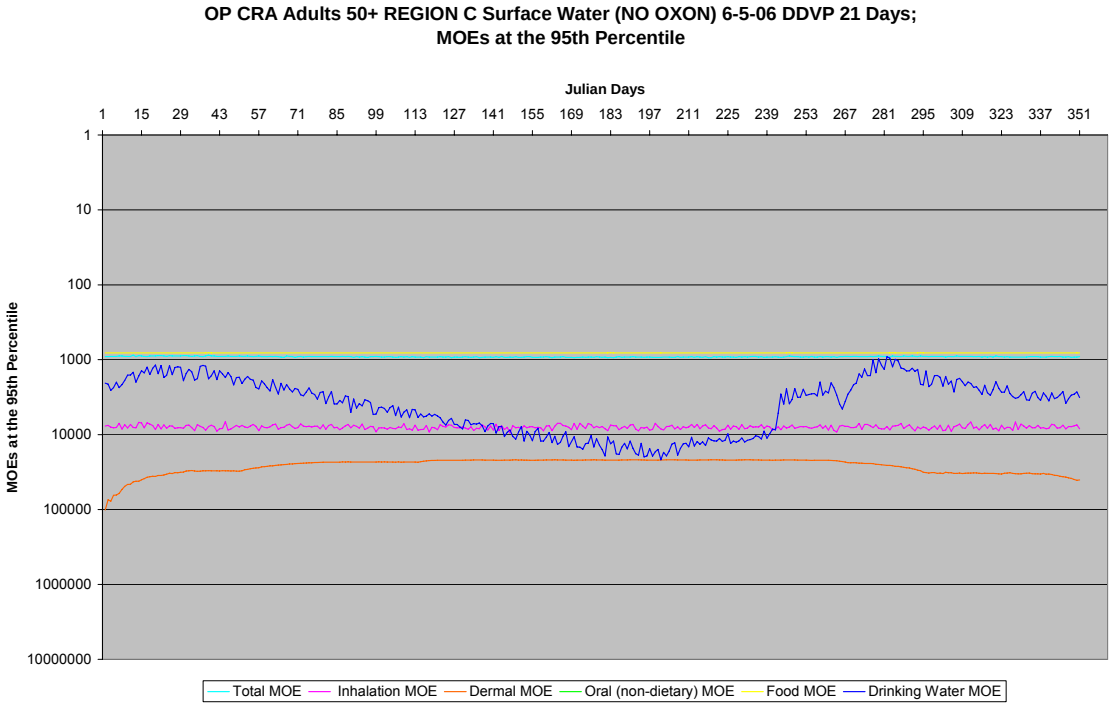


Figure III.B 20

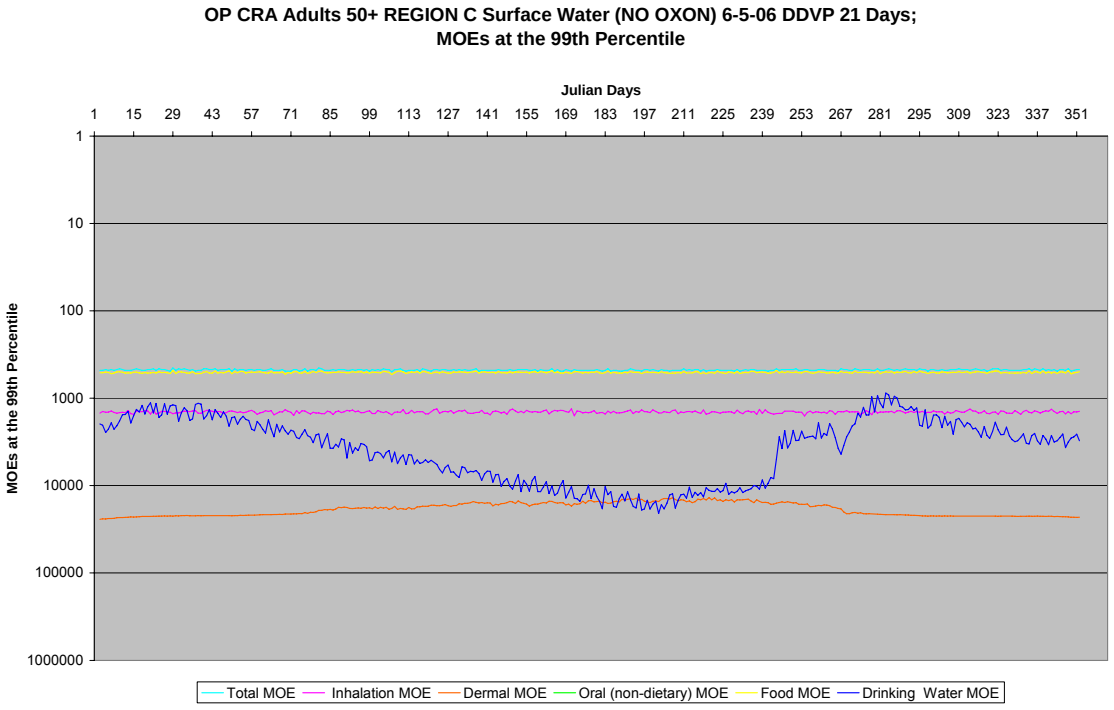


Figure III.B 21

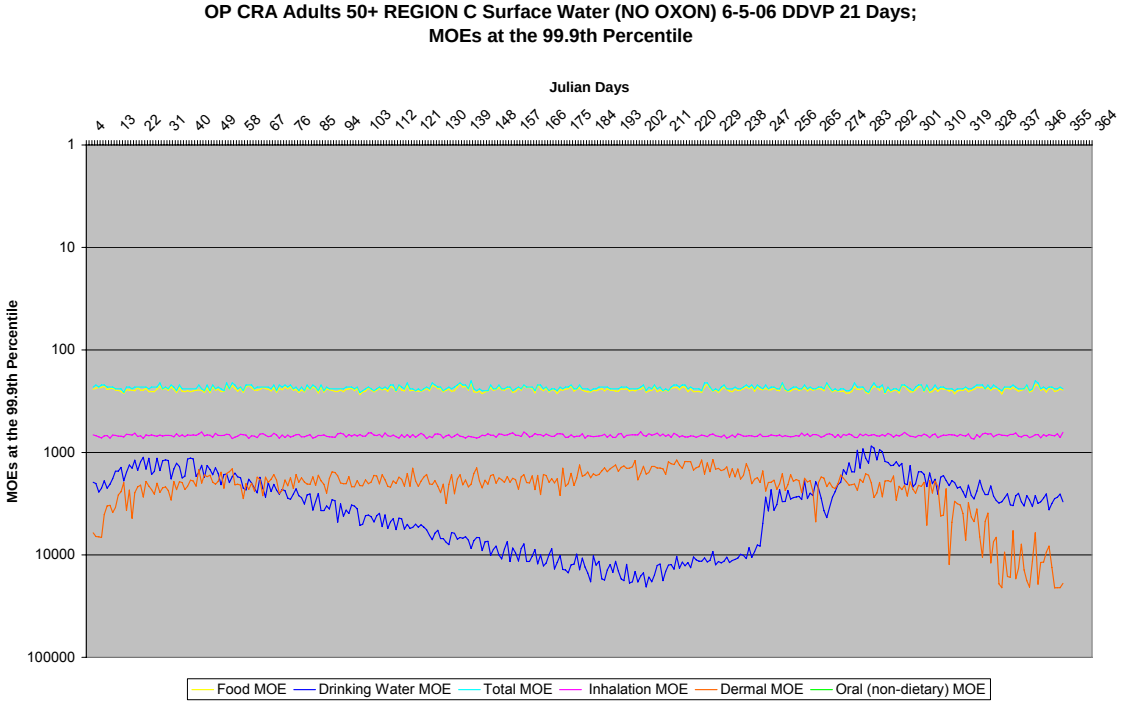


Figure III.B 22

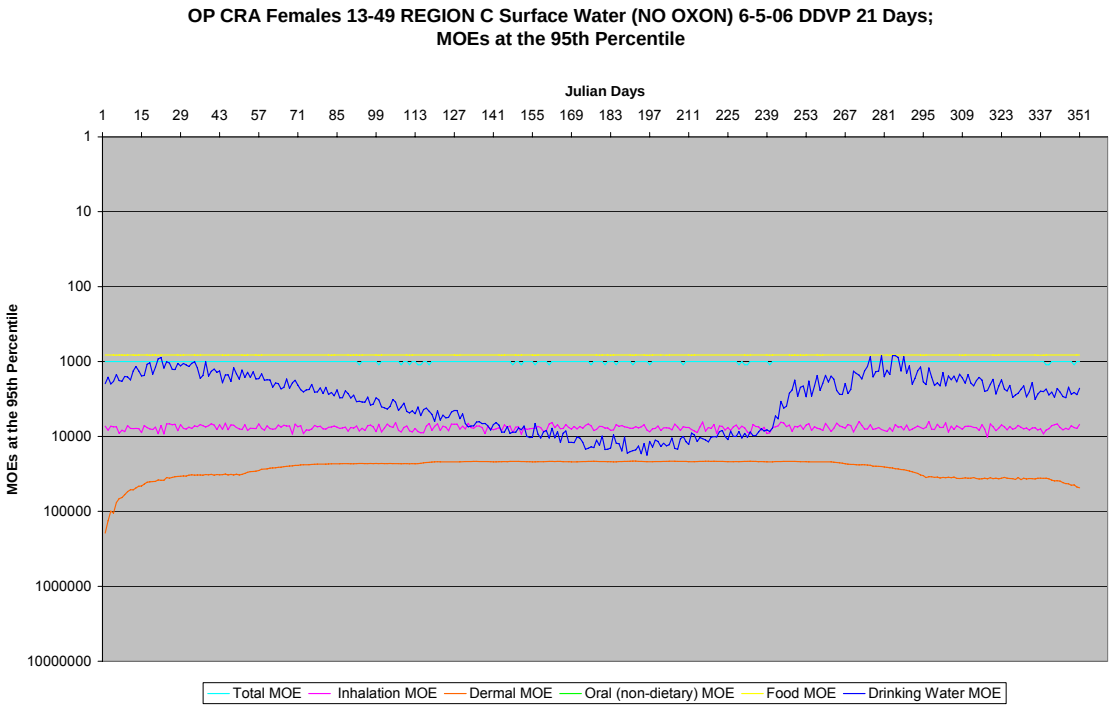


Figure III.B 23

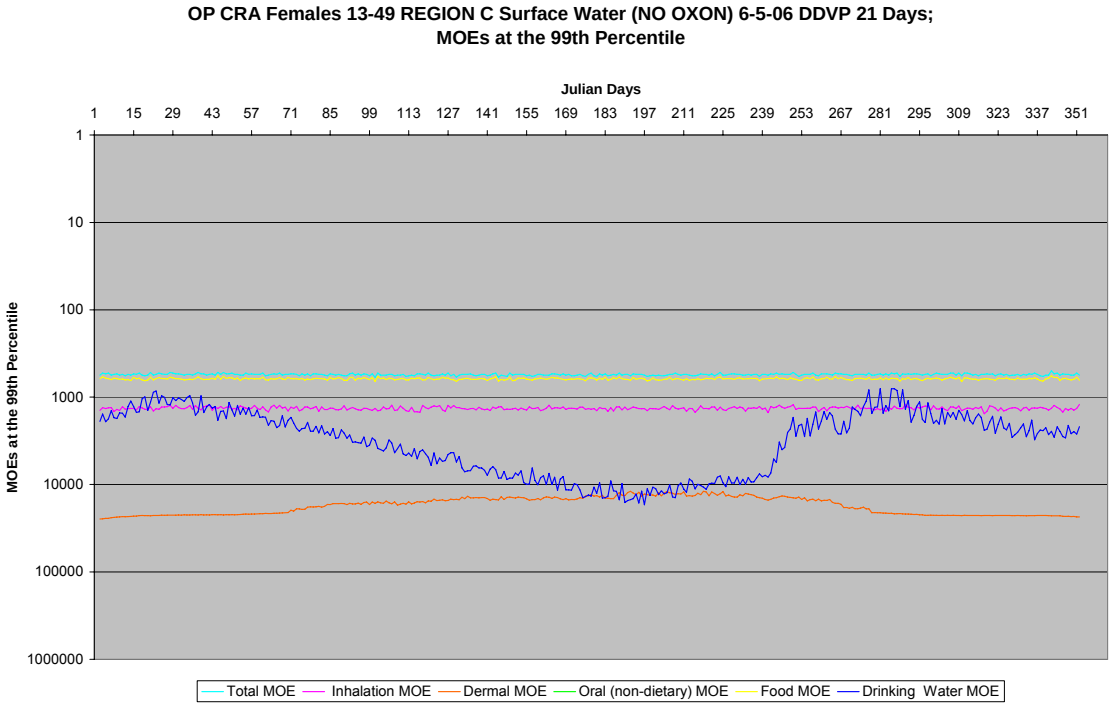
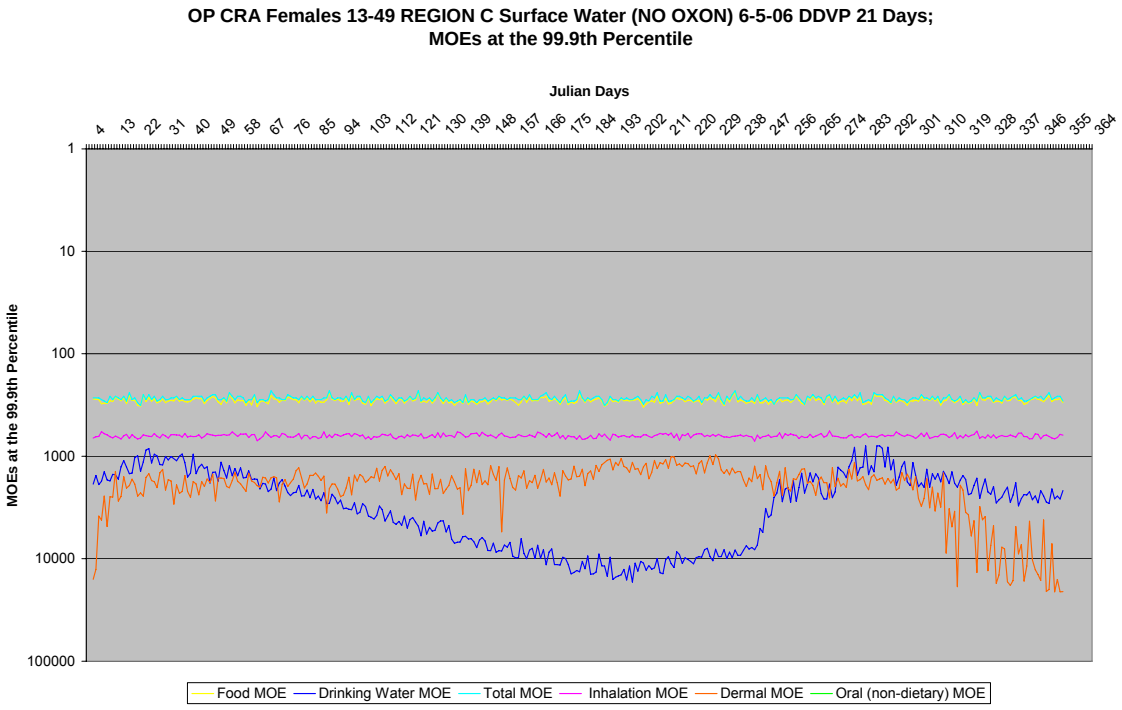


Figure III.B 24



C. Region C 10x

Figure III.C 1

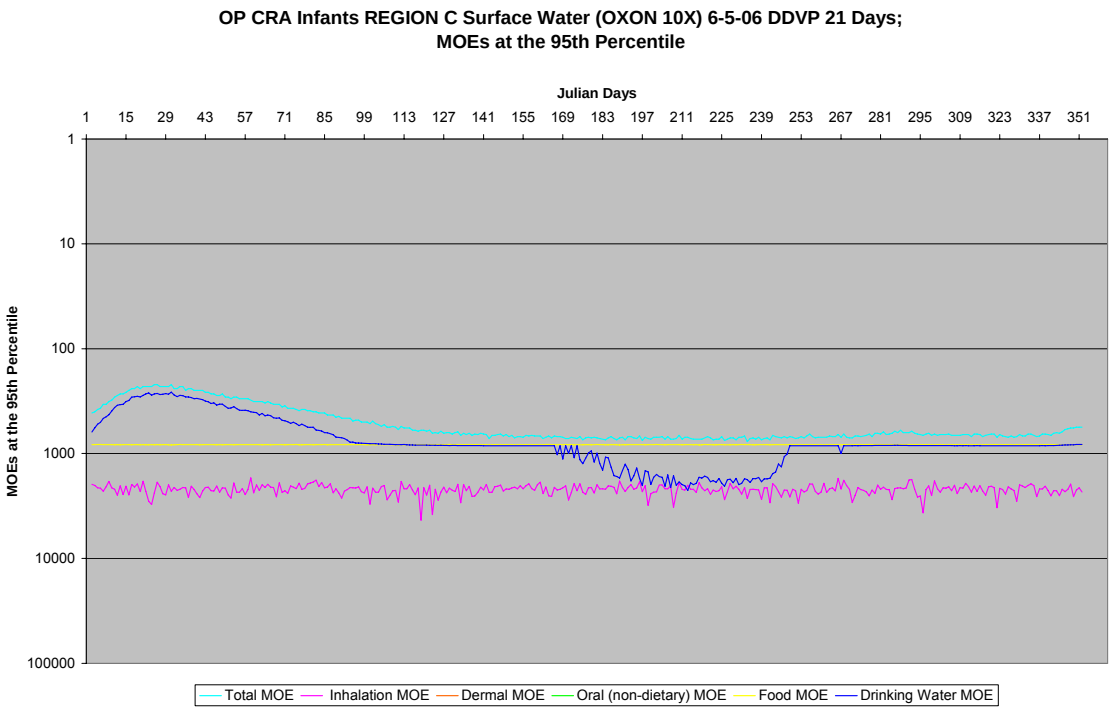


Figure III.C 2

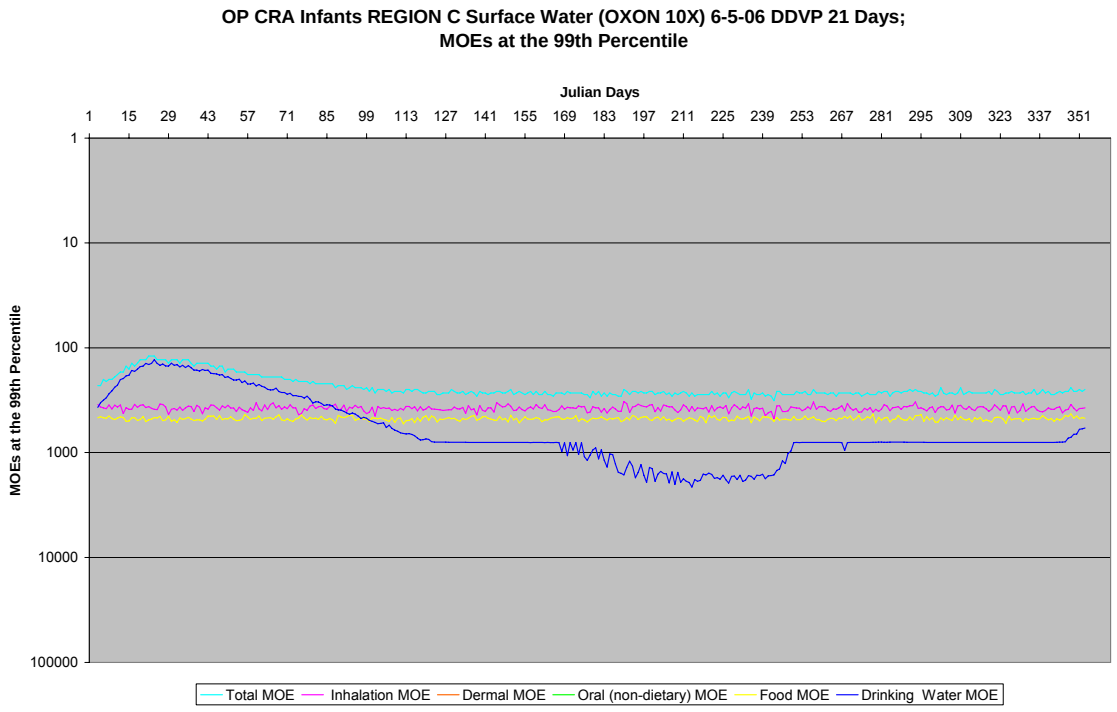


Figure III.C 3

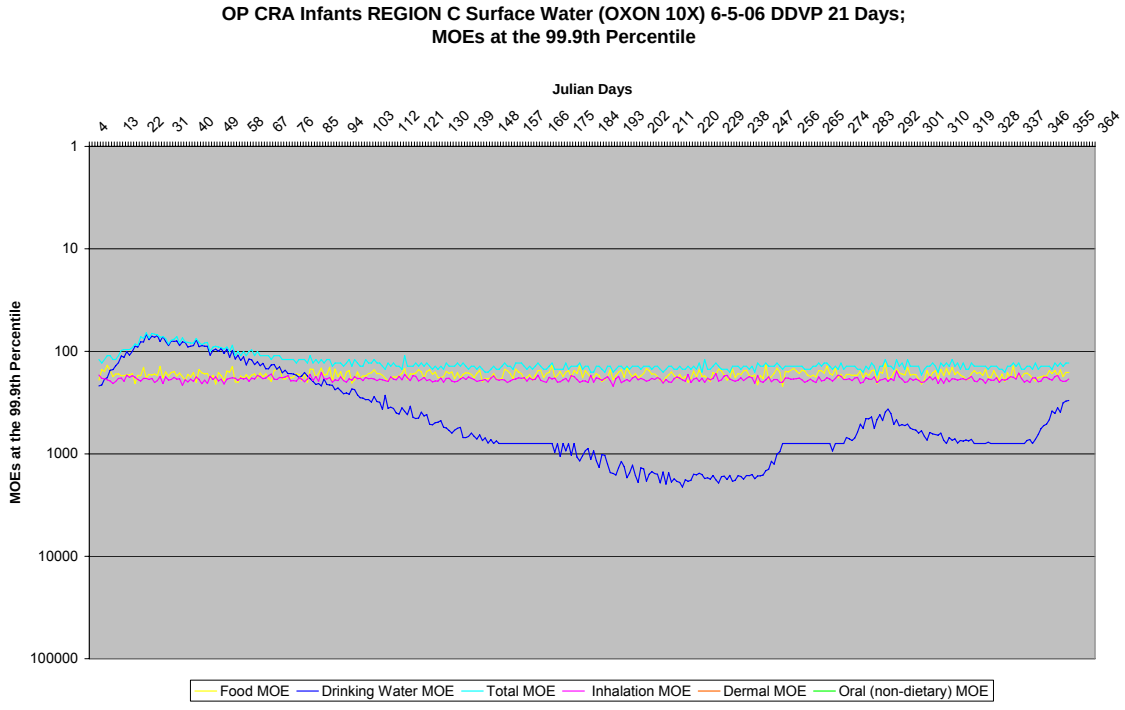


Figure III.C 4

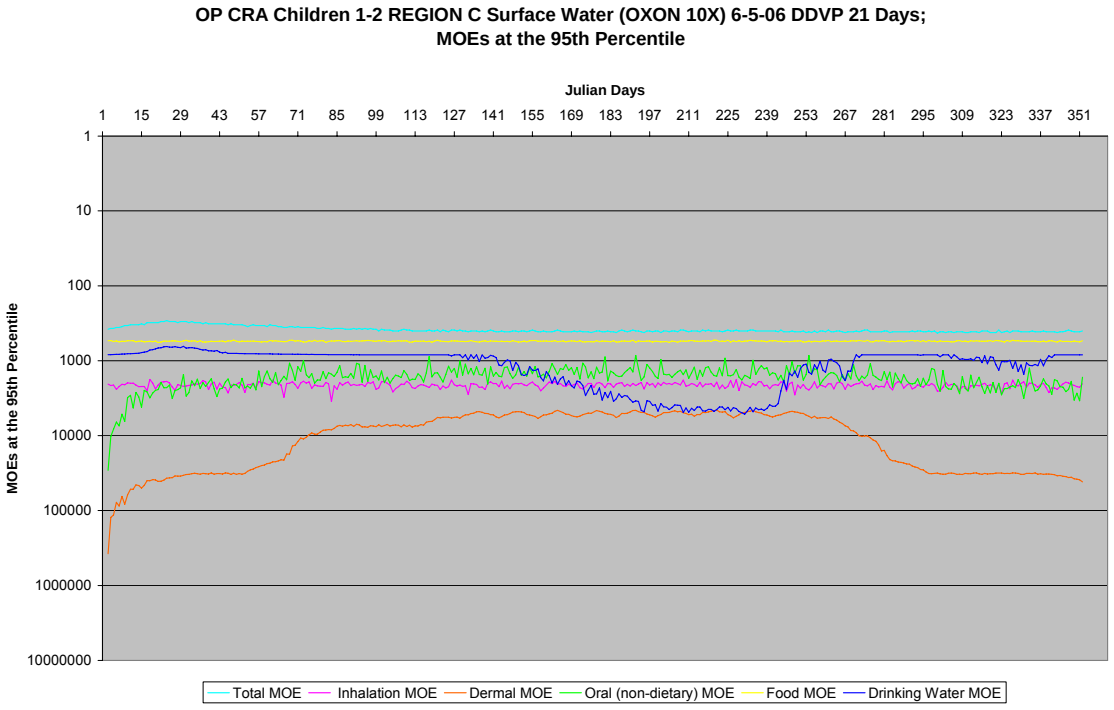


Figure III.C 5

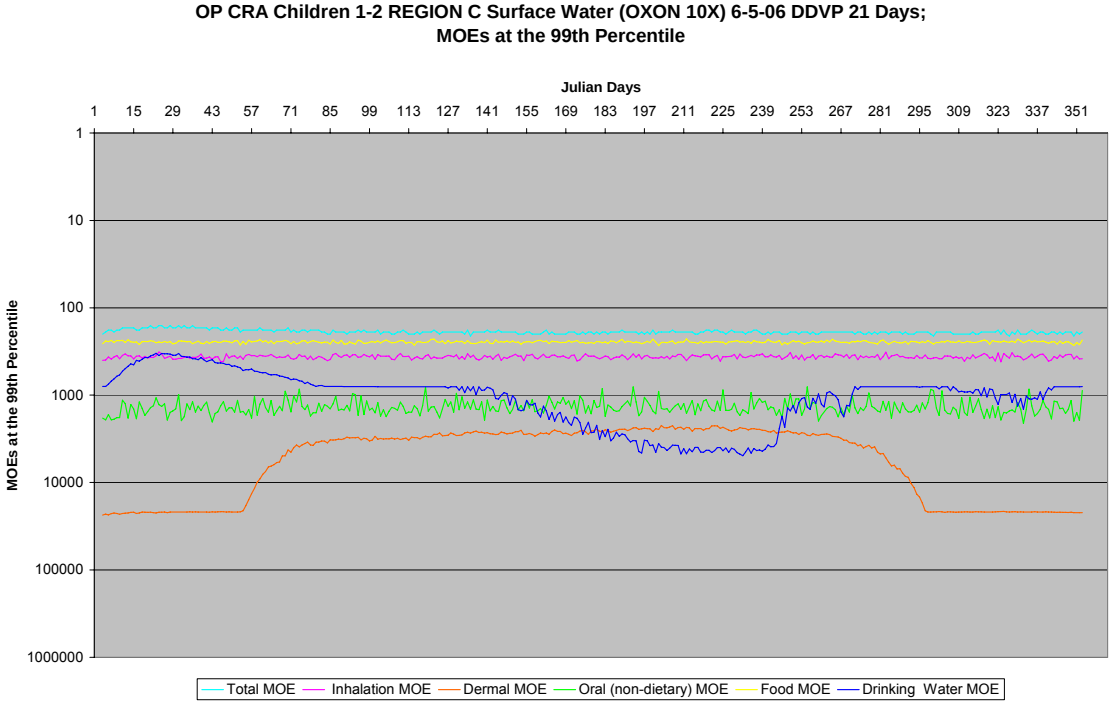


Figure III.C 6

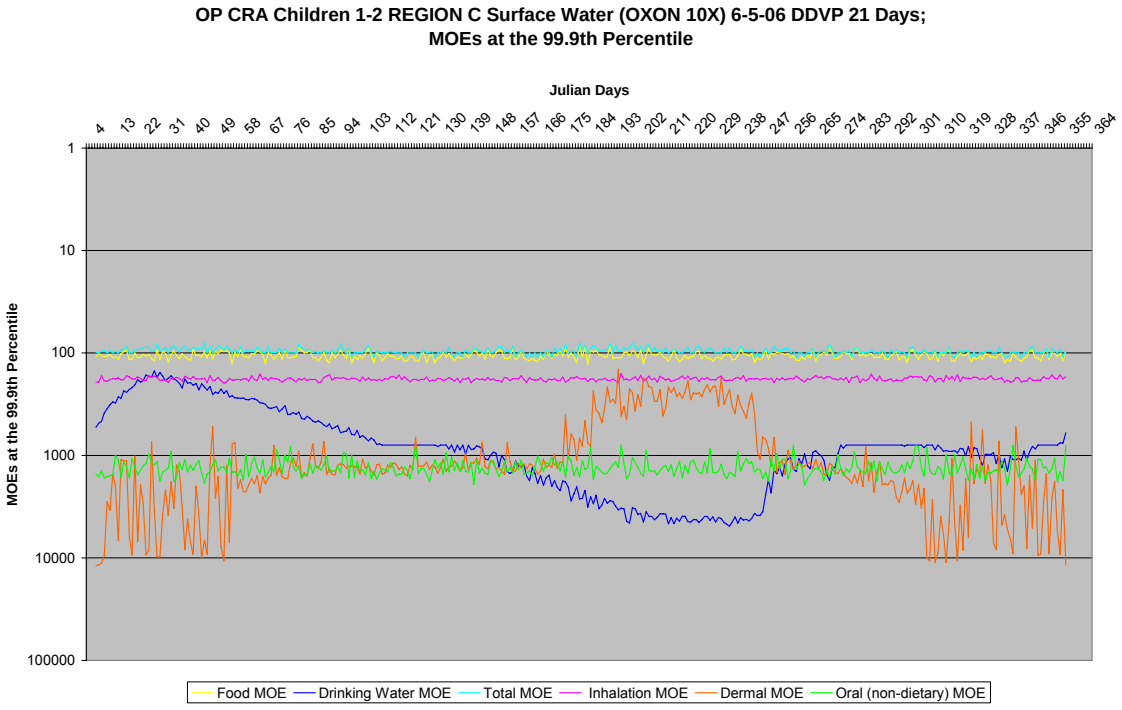


Figure III.C 7

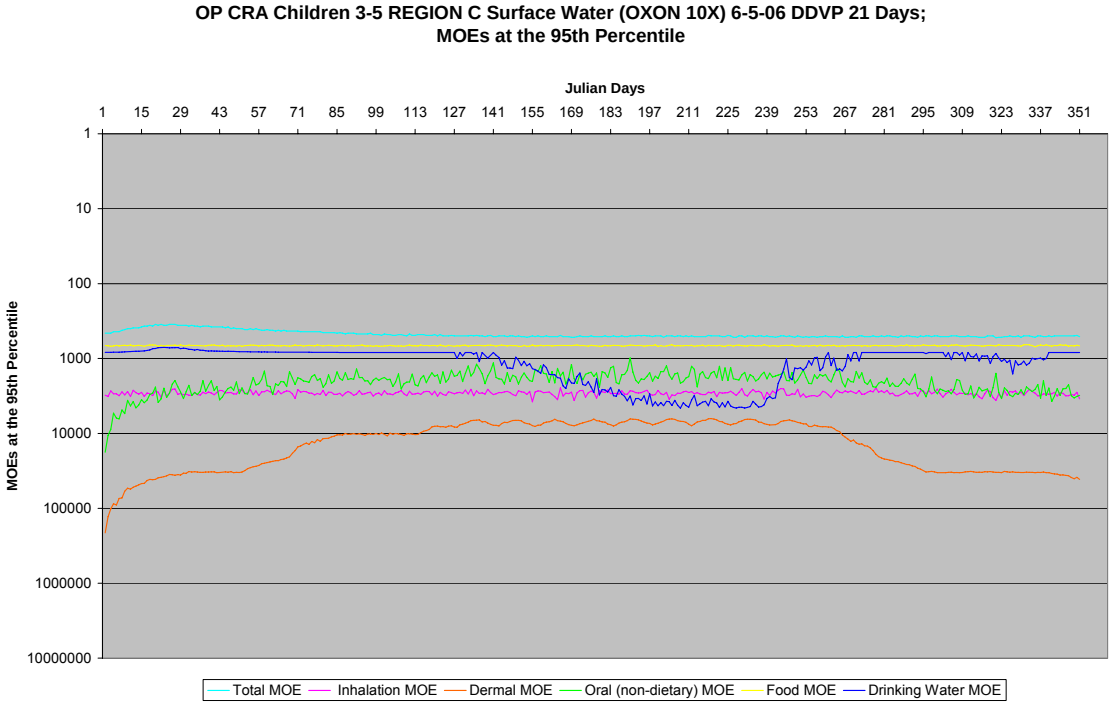


Figure III.C 8

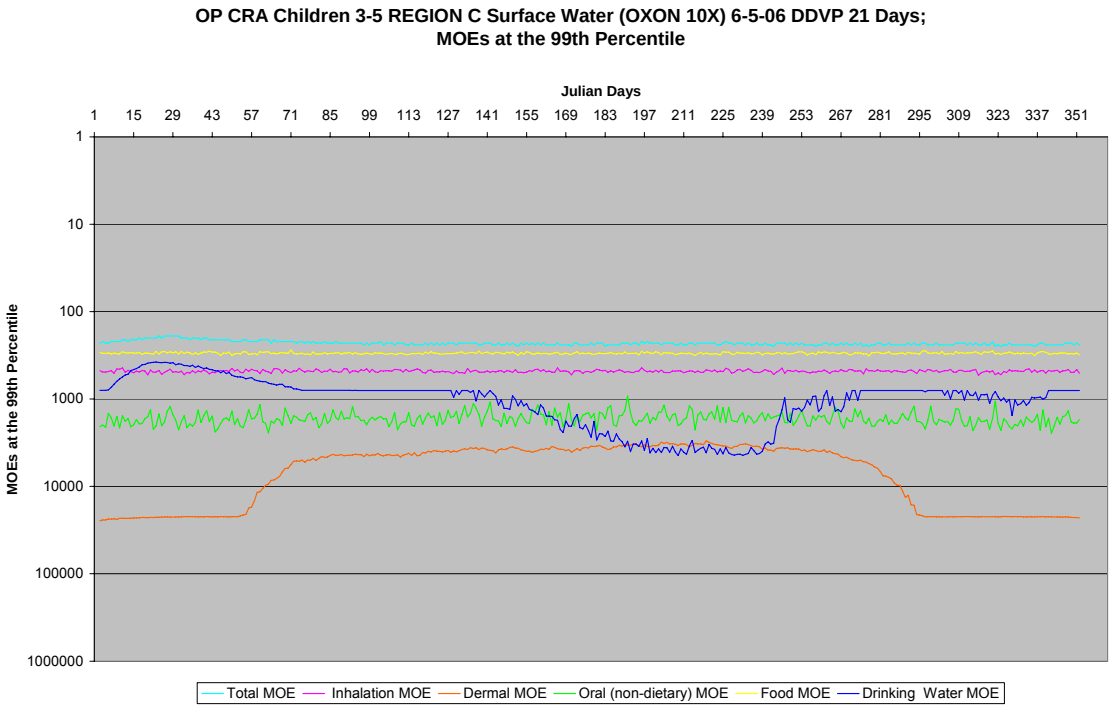


Figure III.C 9

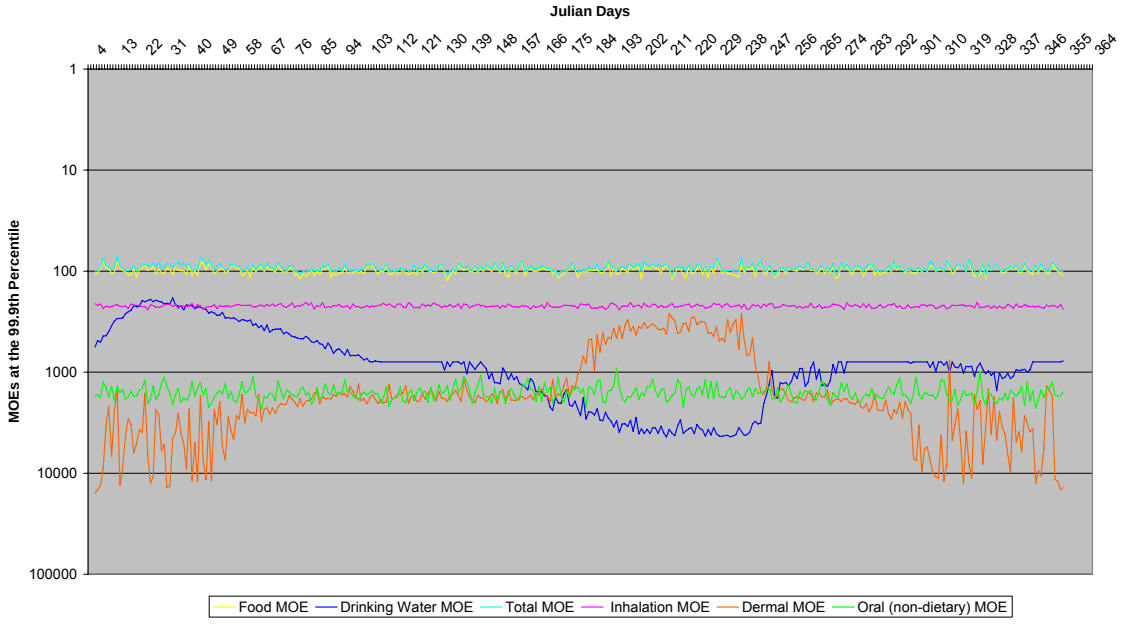


Figure III.C 10

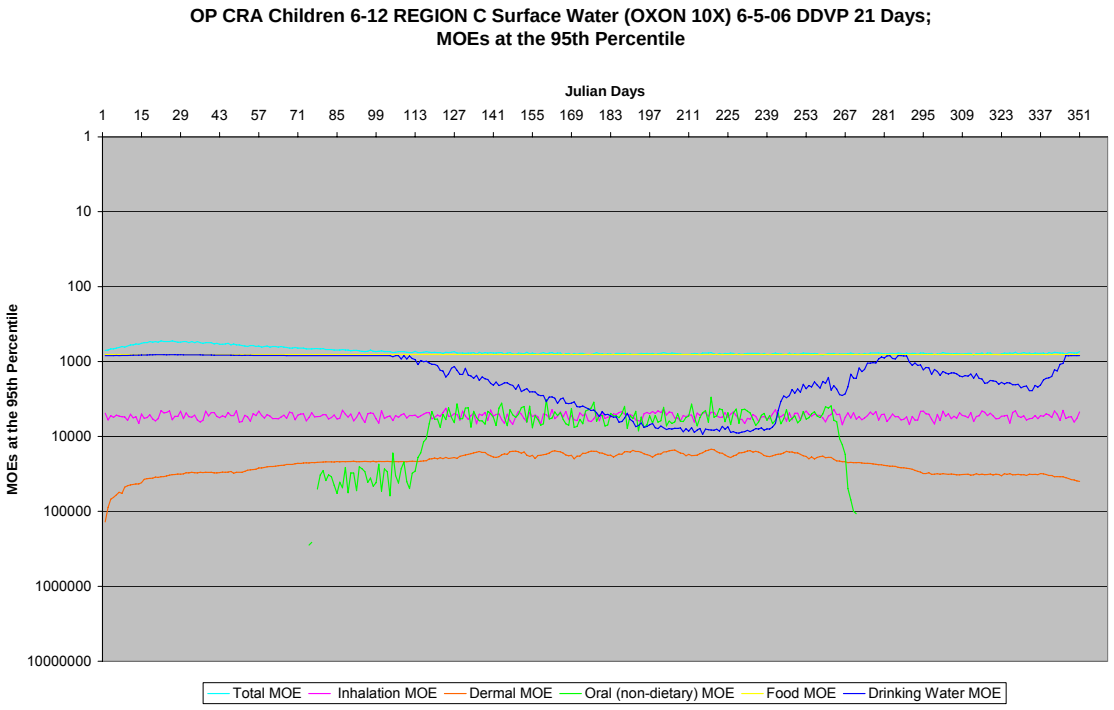


Figure III.C 11

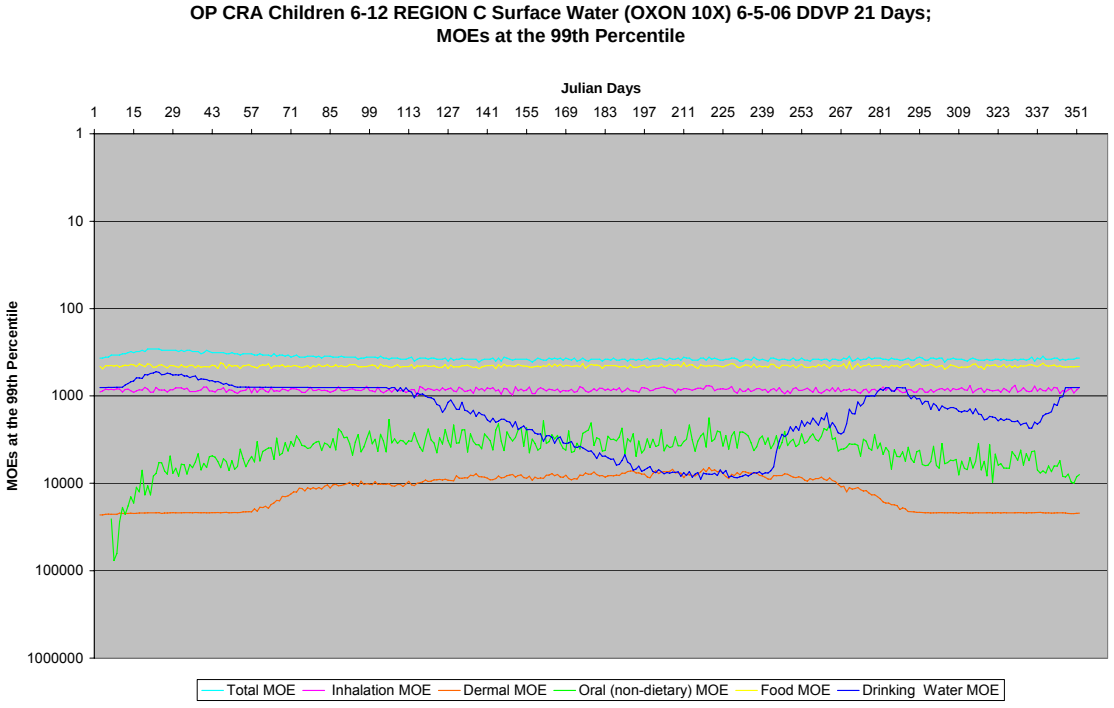


Figure III.C 12

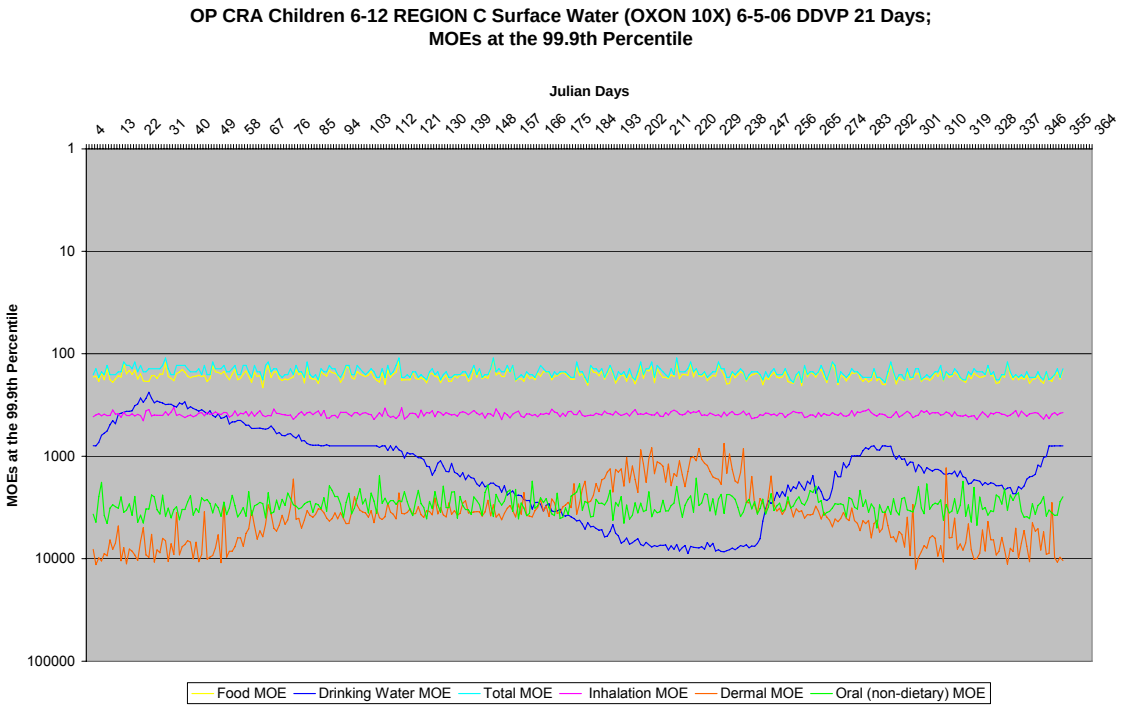


Figure III.C 13

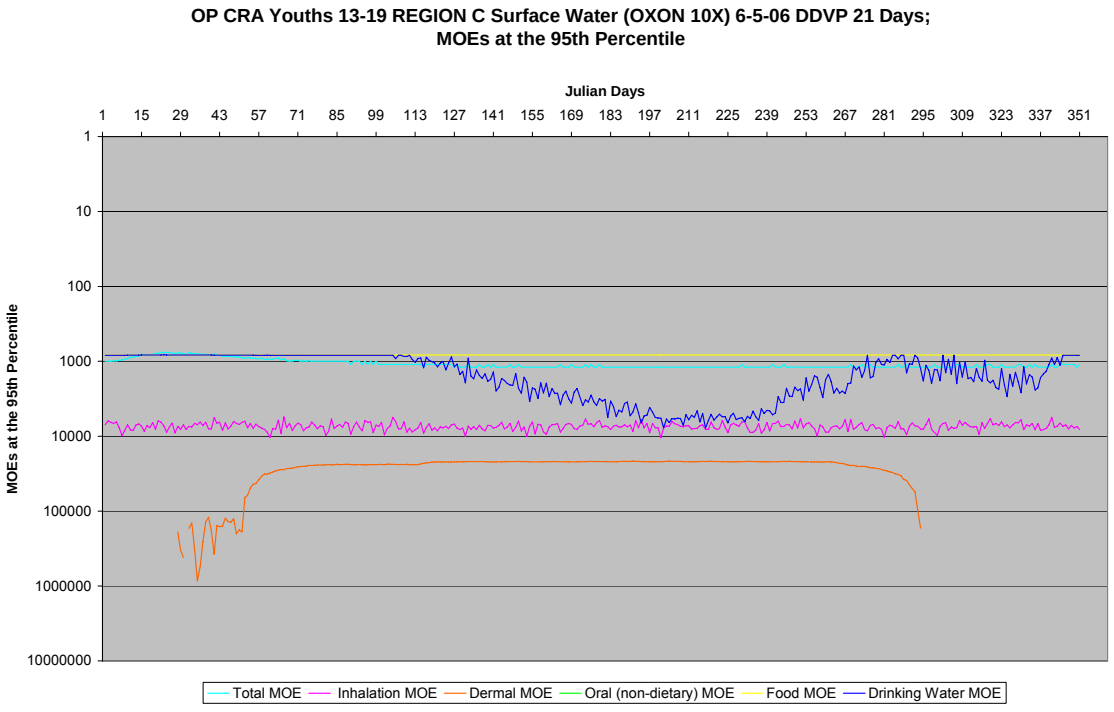
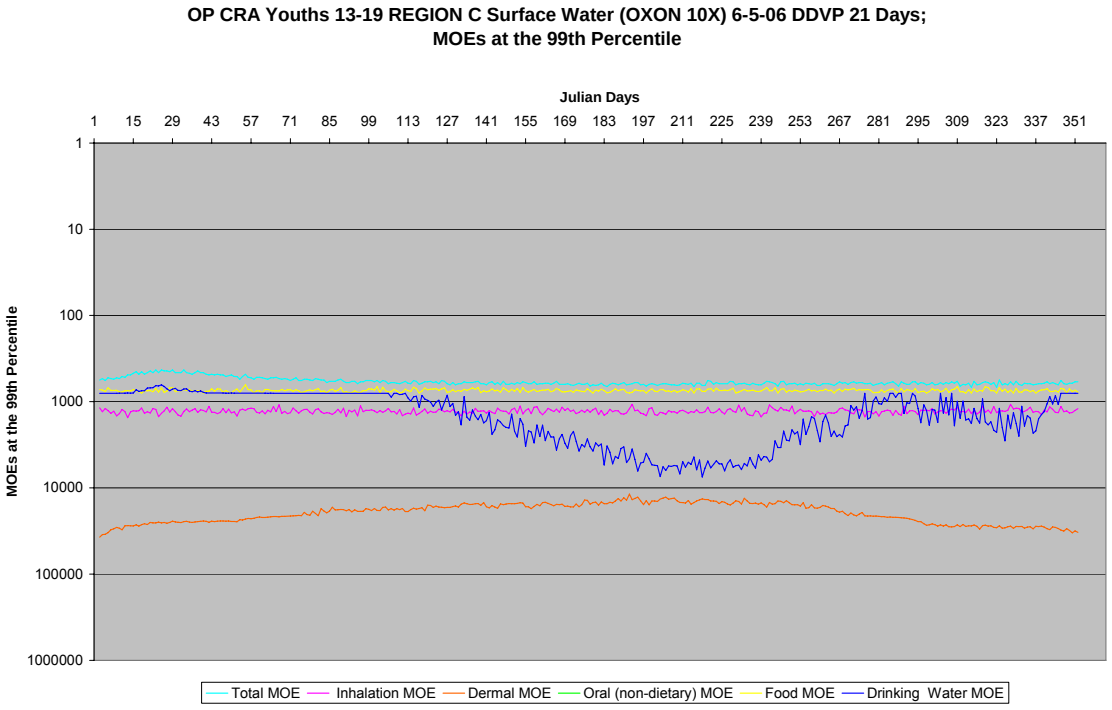


Figure III.C 14



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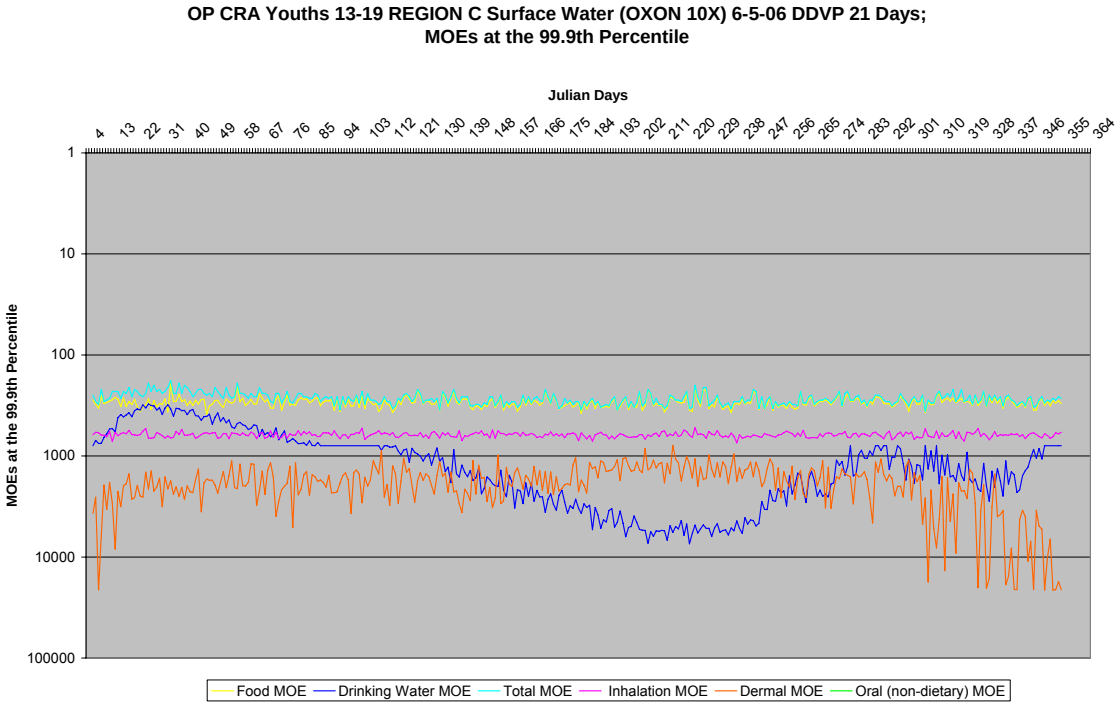

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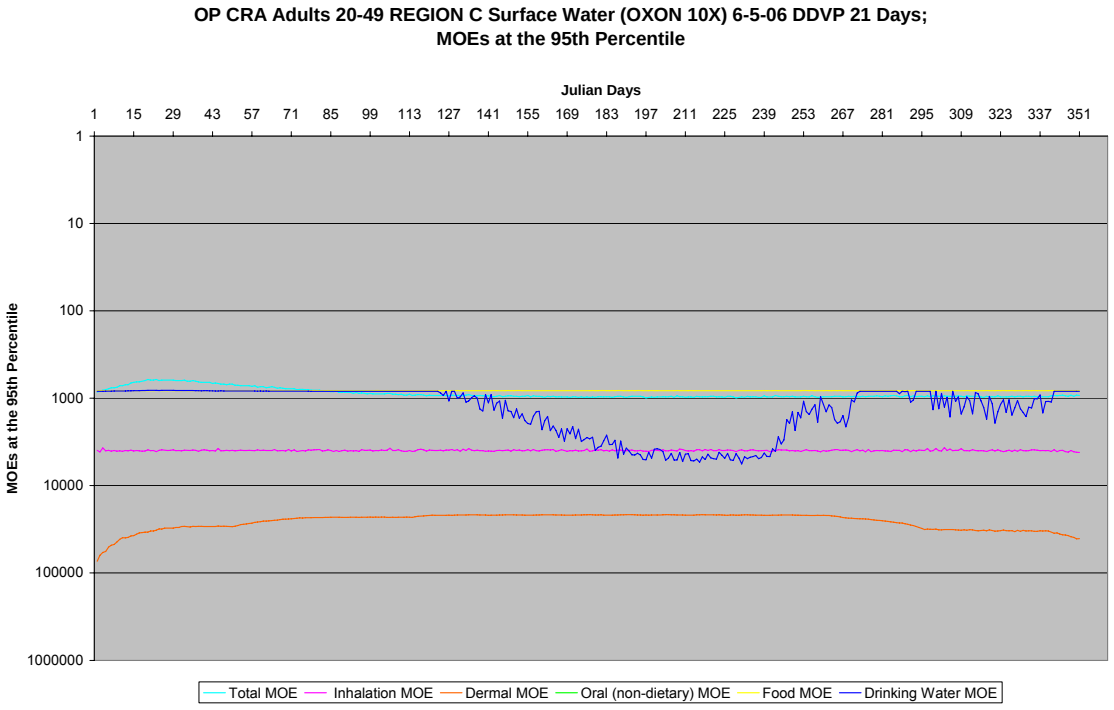

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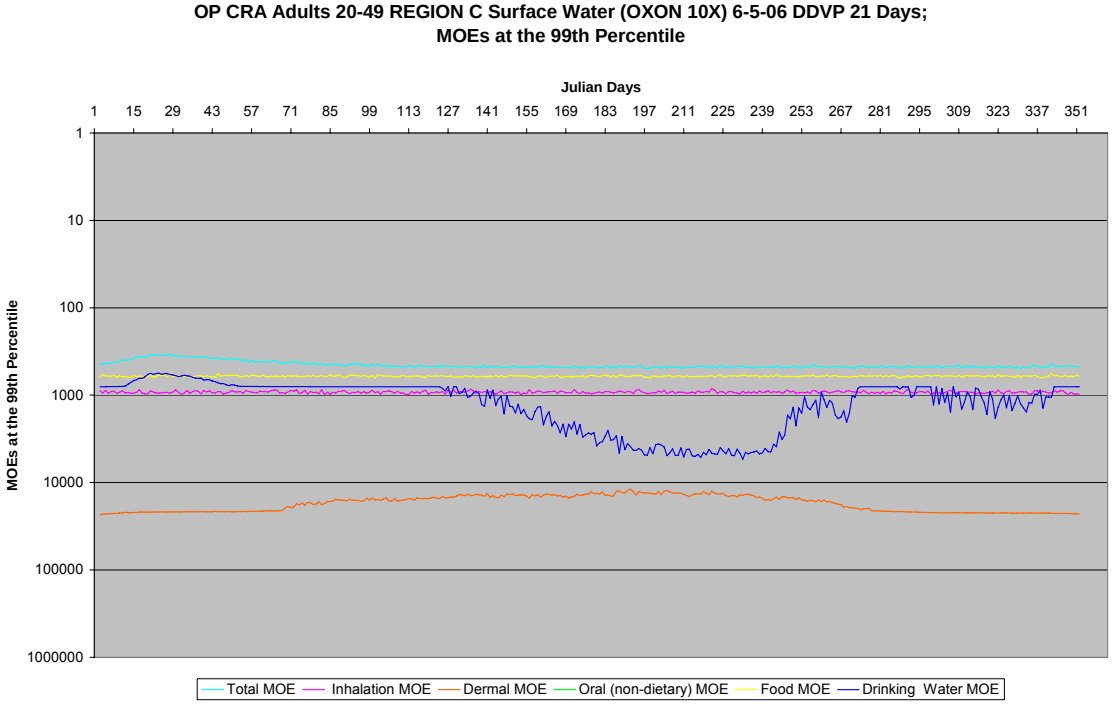
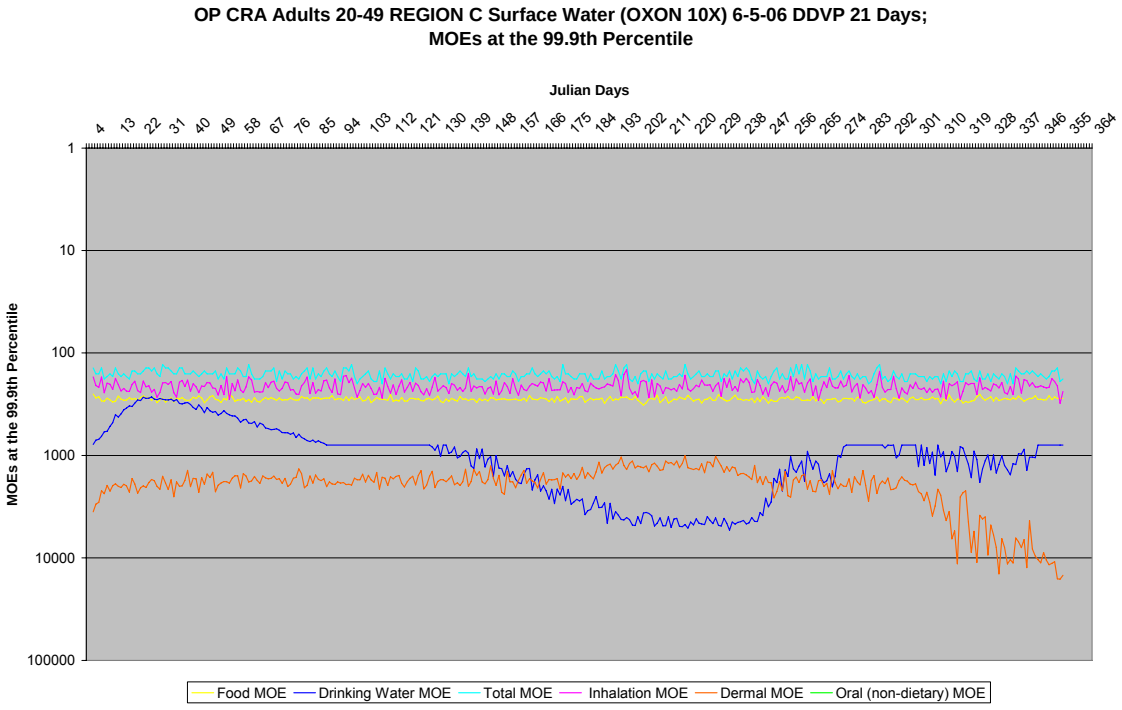


Figure III.C 18



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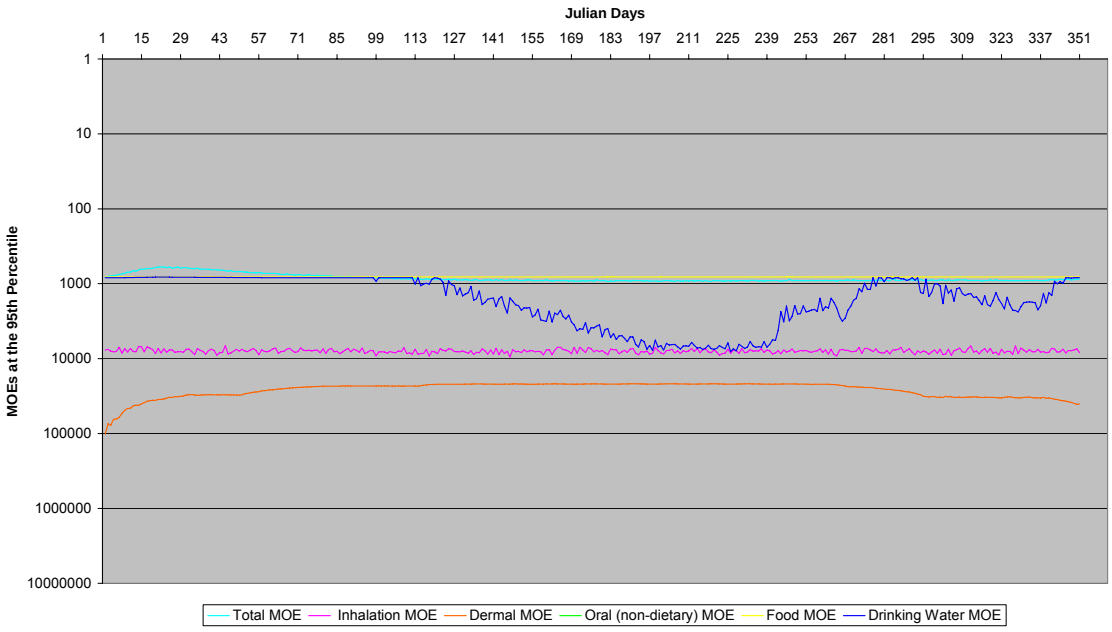

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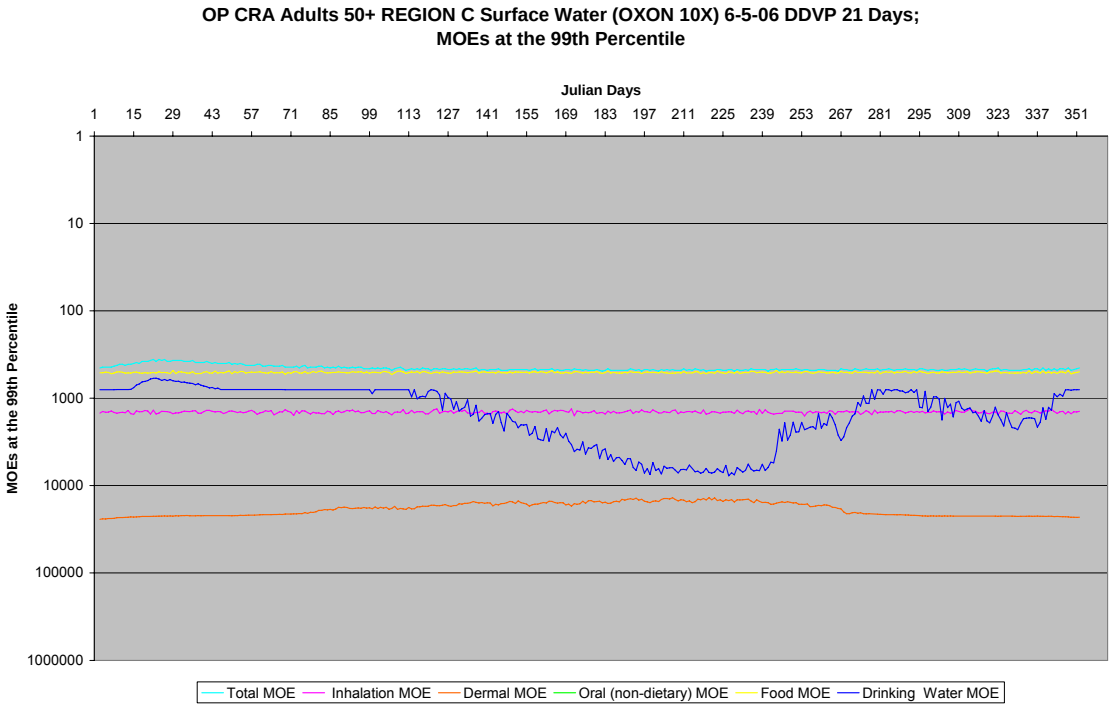

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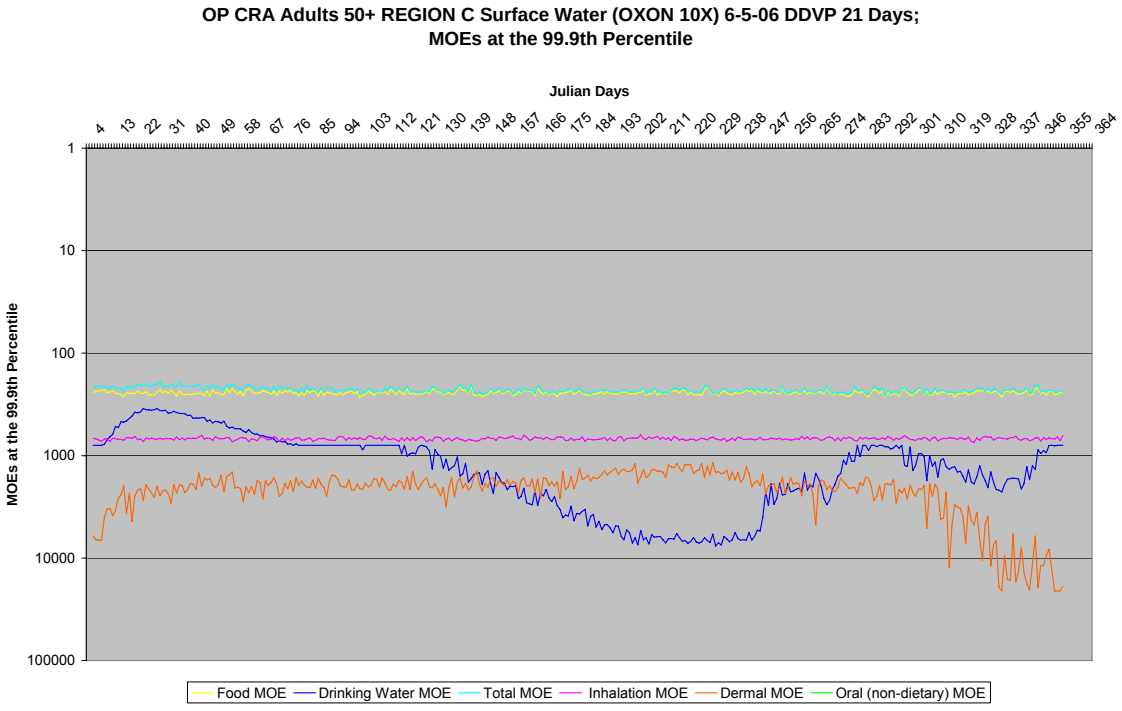

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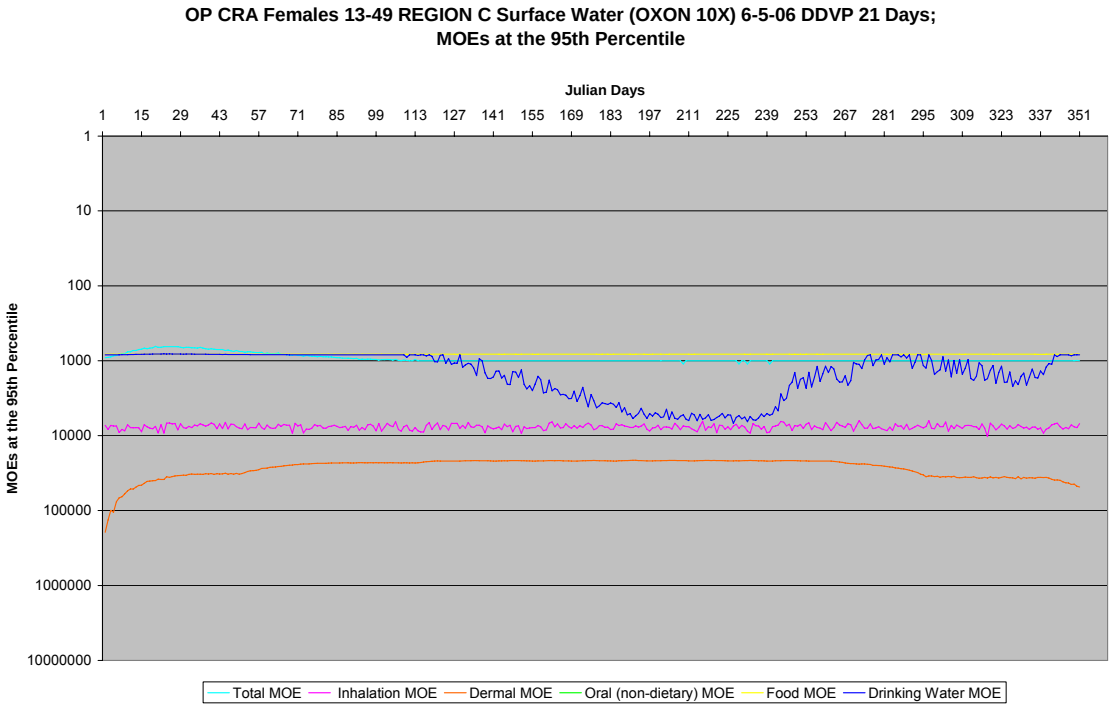

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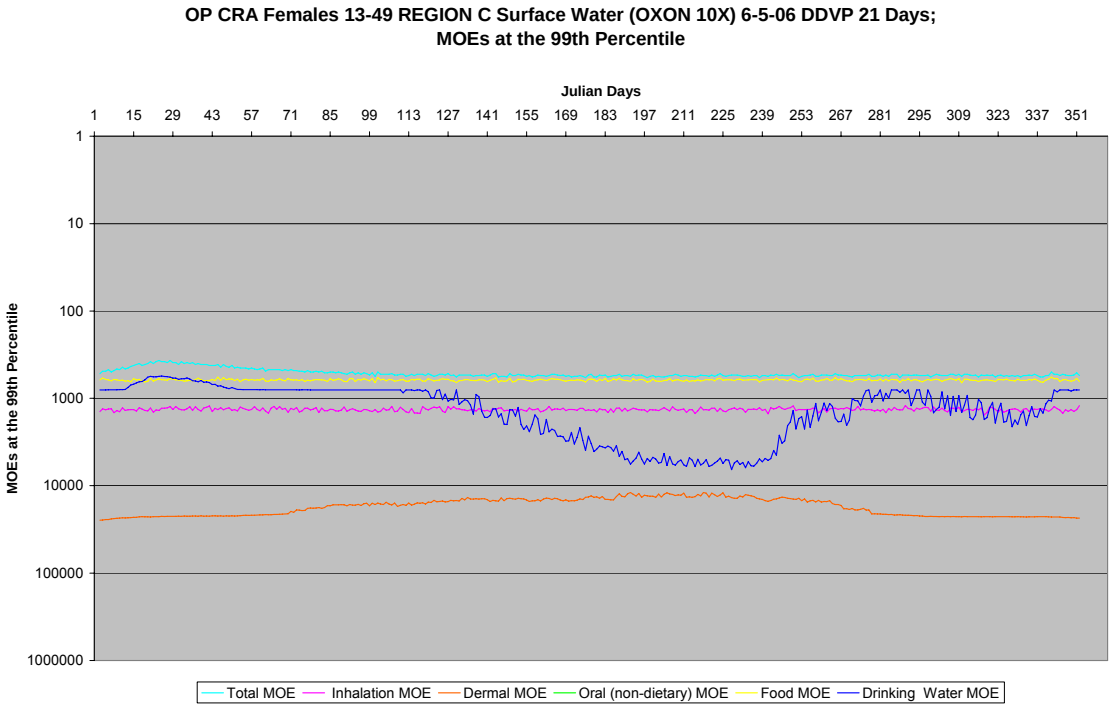
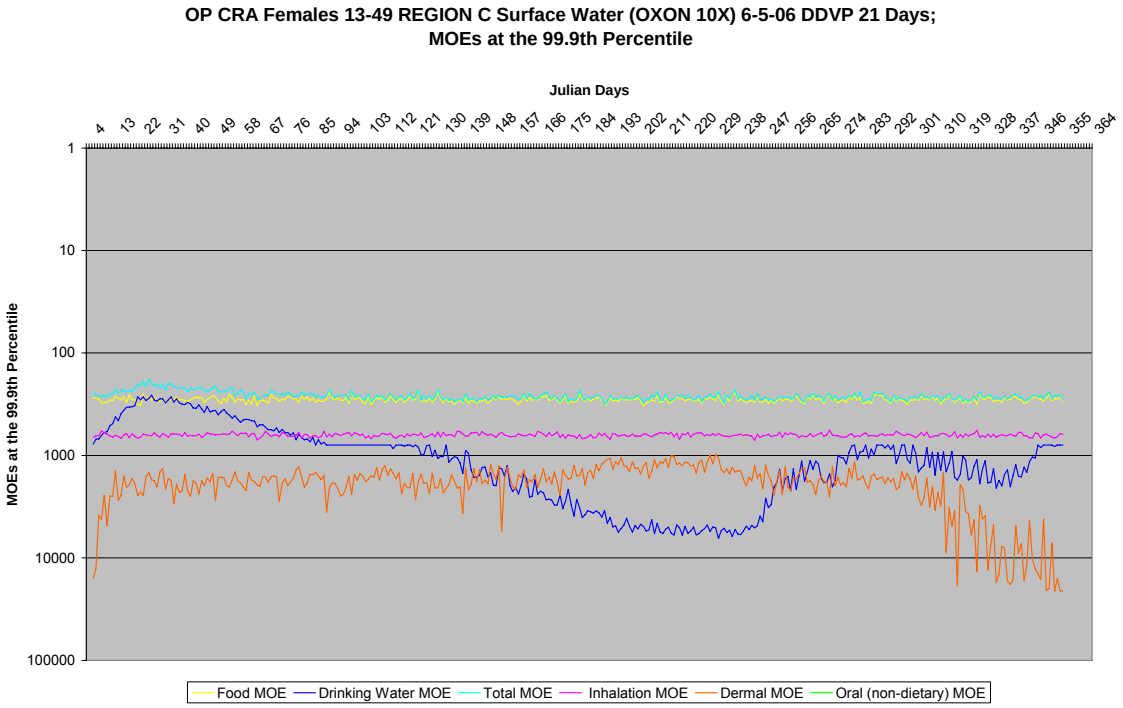


Figure III.C 24



D. Region C 100x

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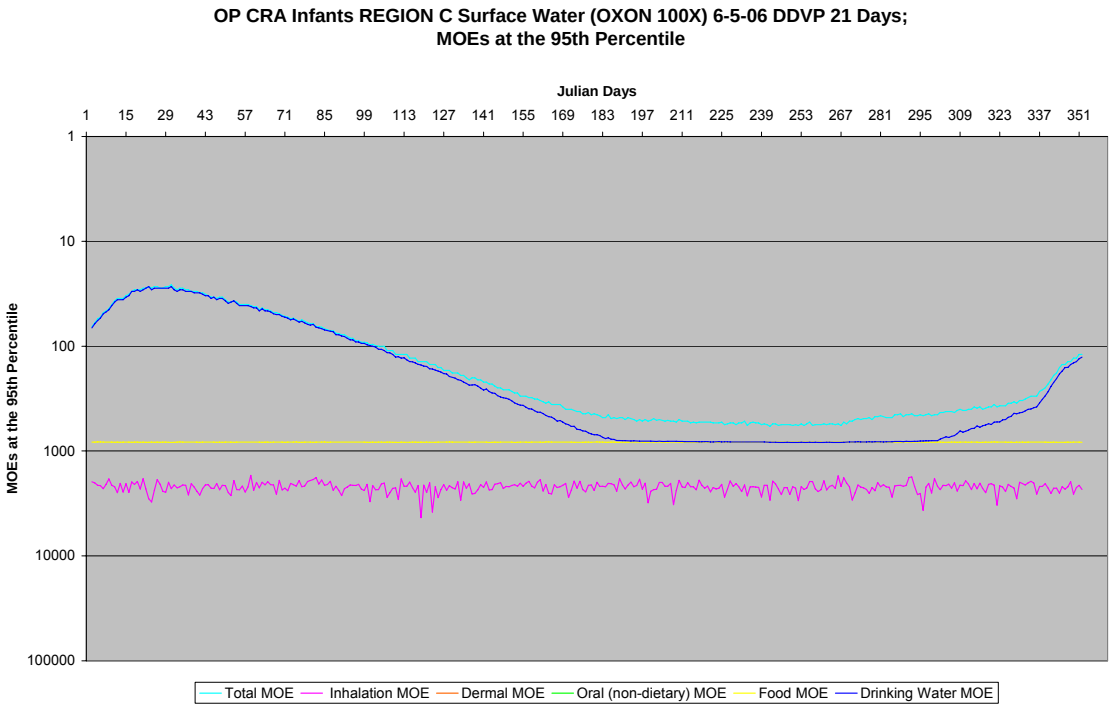

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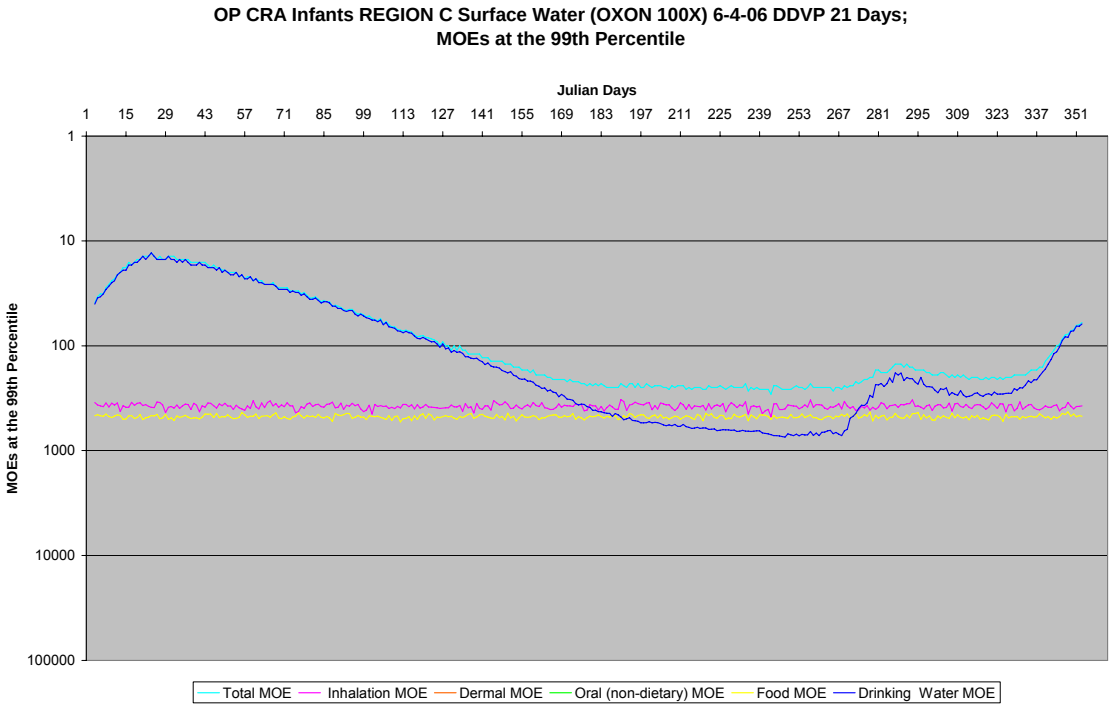

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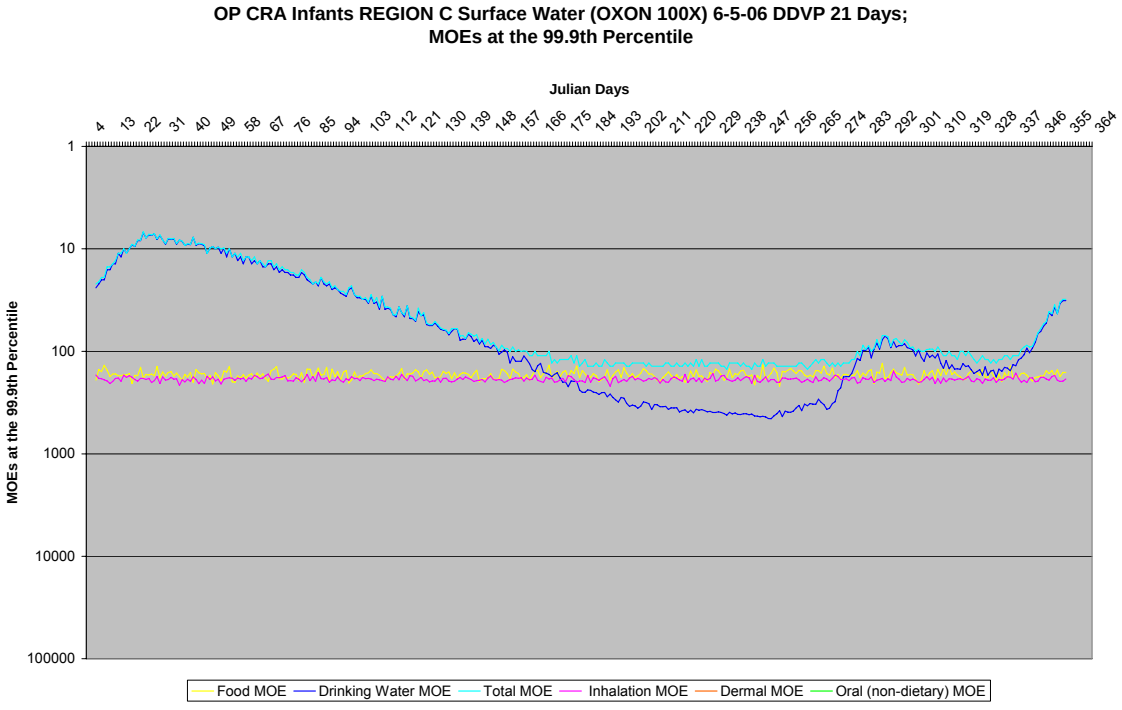

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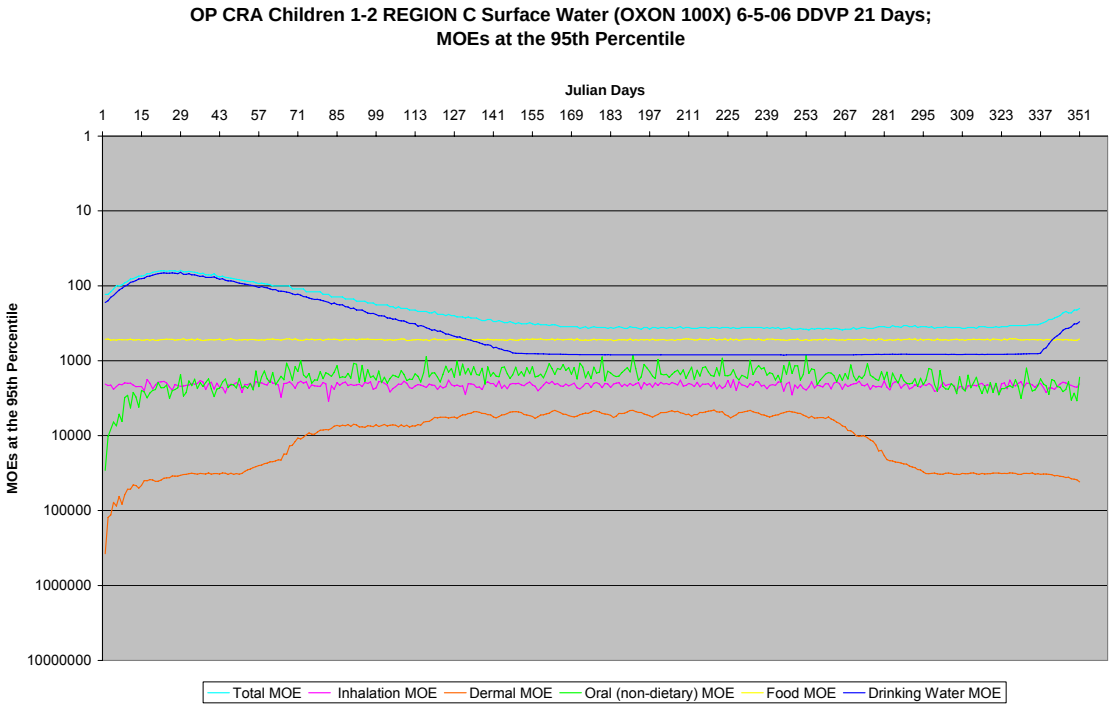


Figure III.D 5

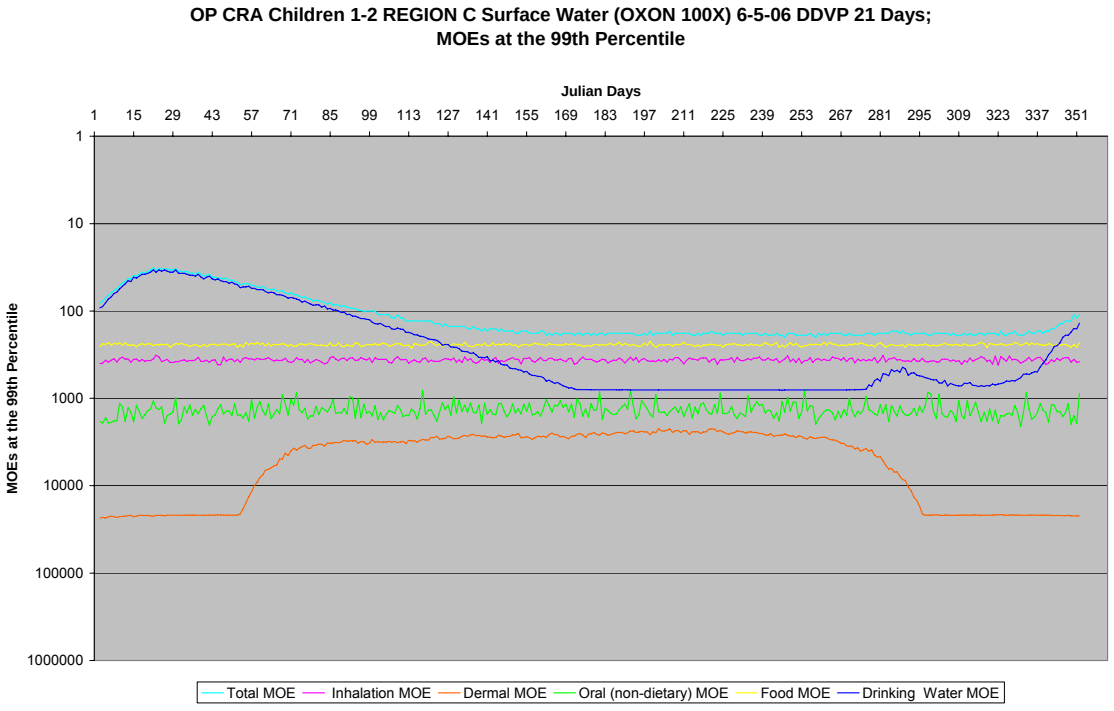
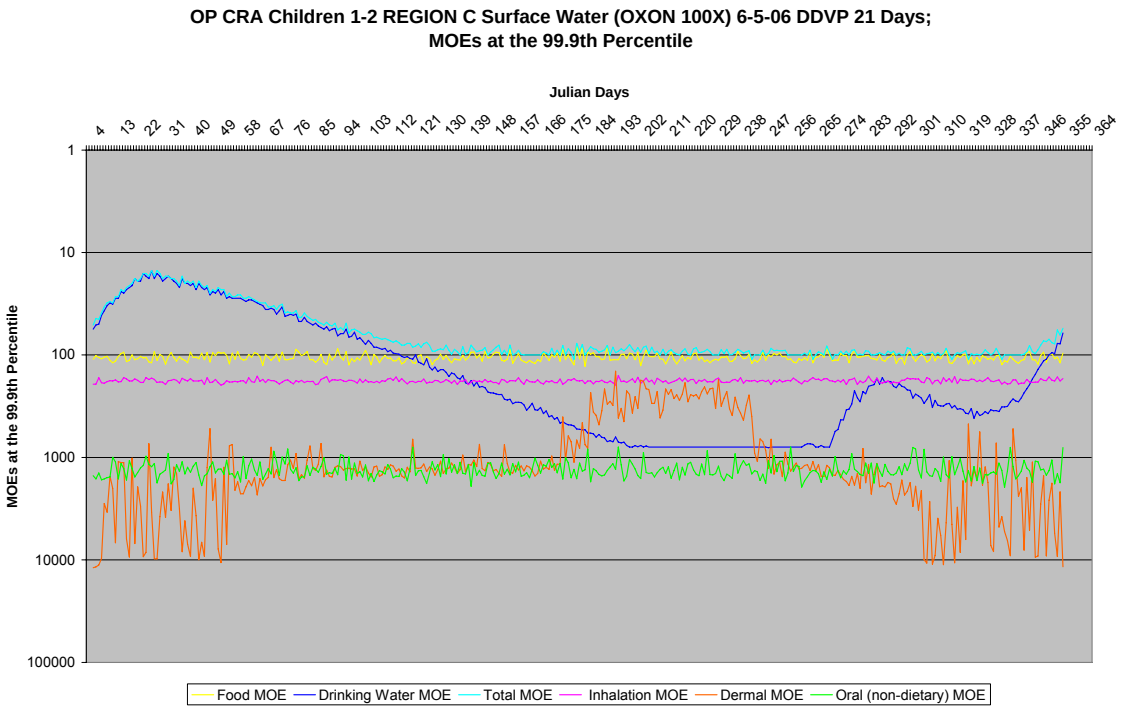


Figure III.D 6



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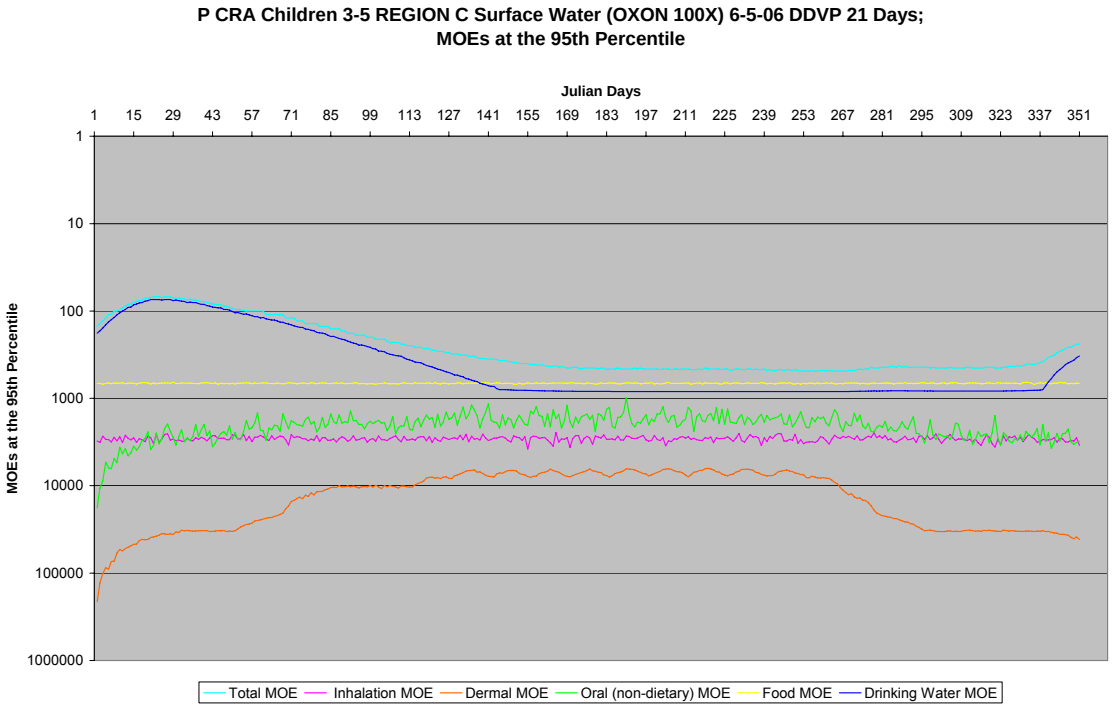
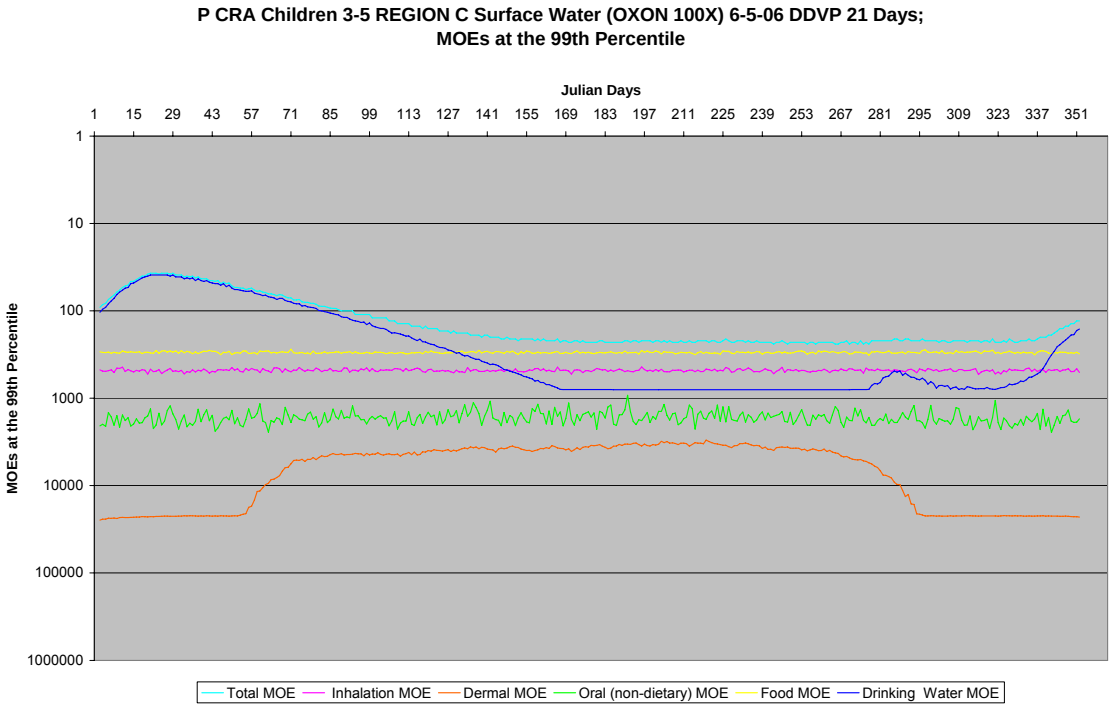


Figure III.D 8



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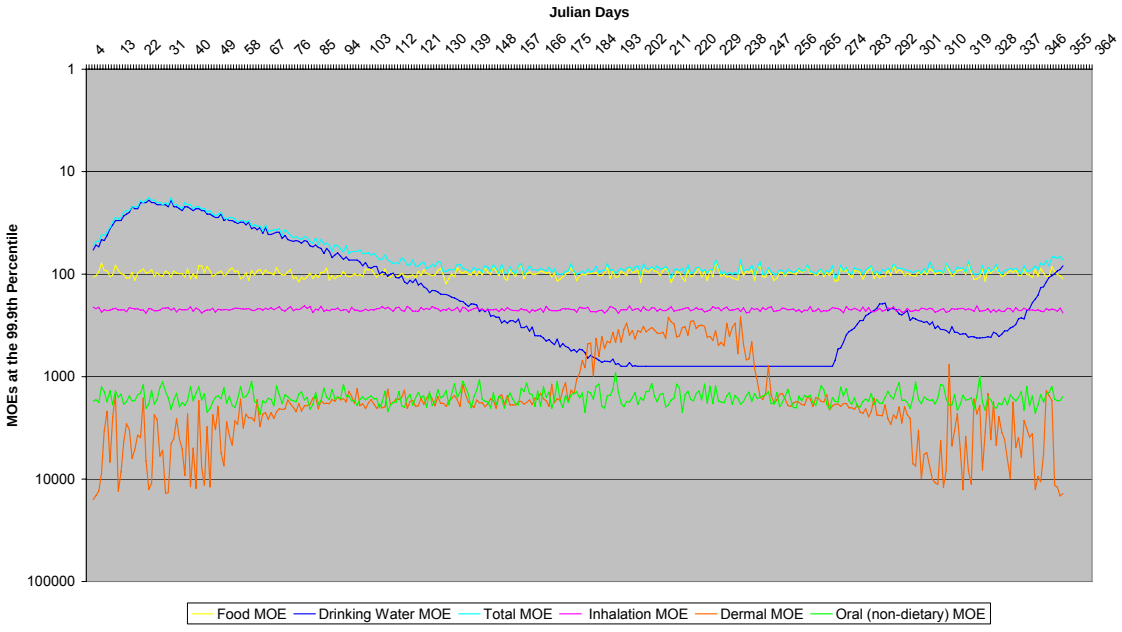

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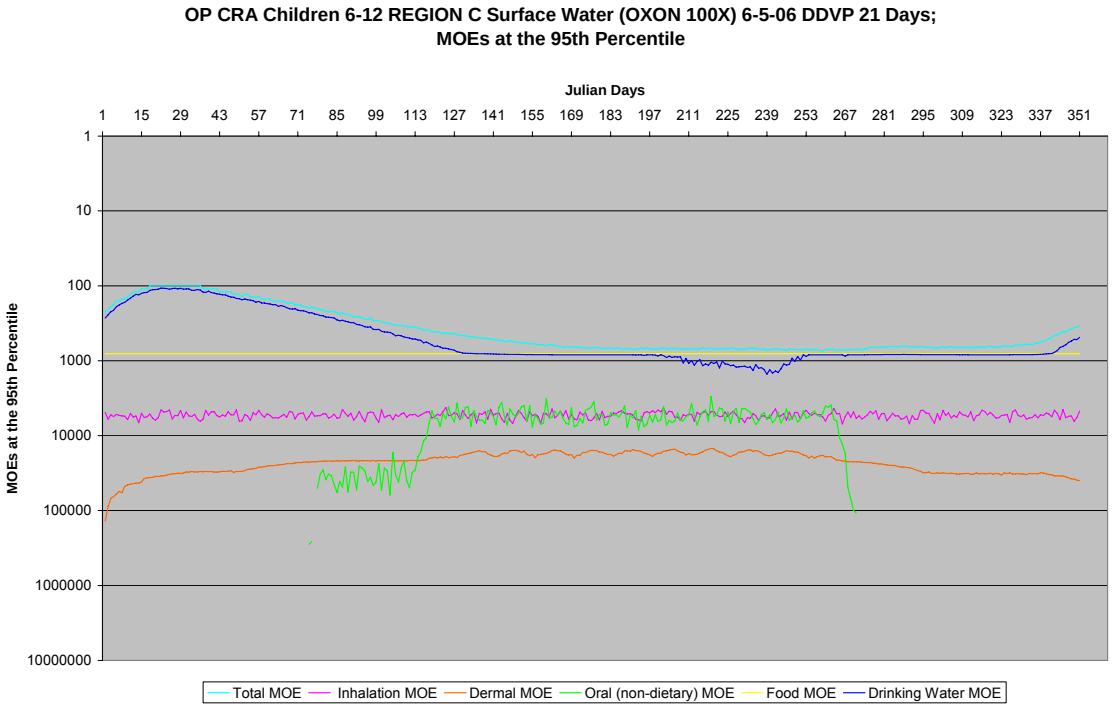

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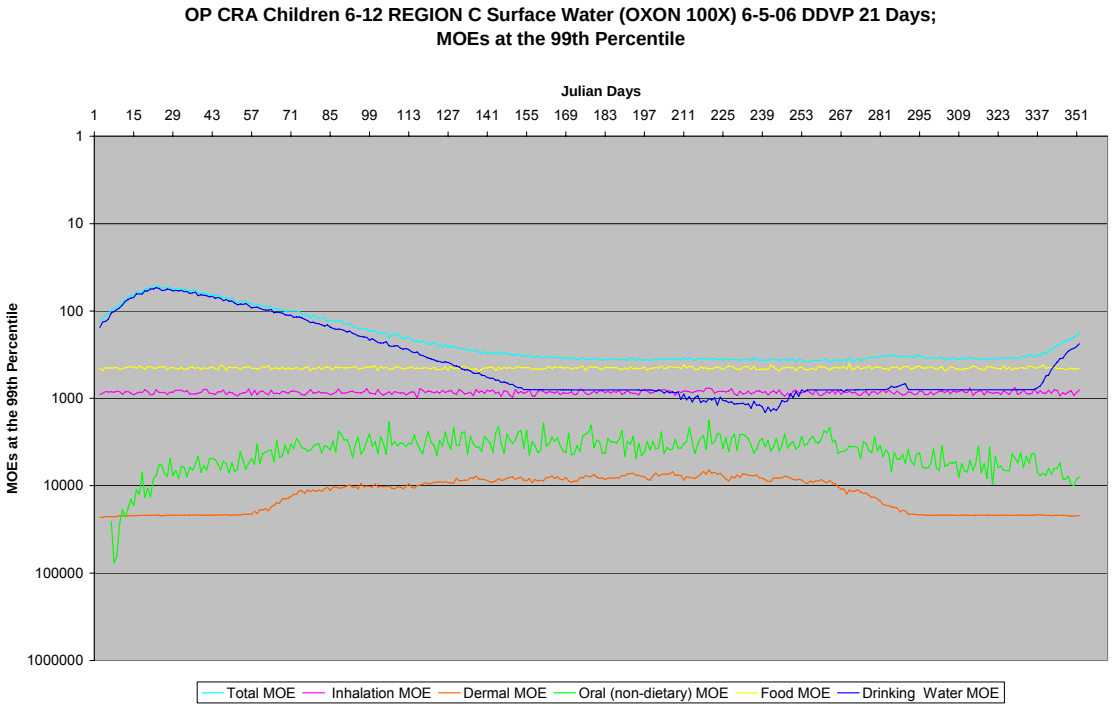

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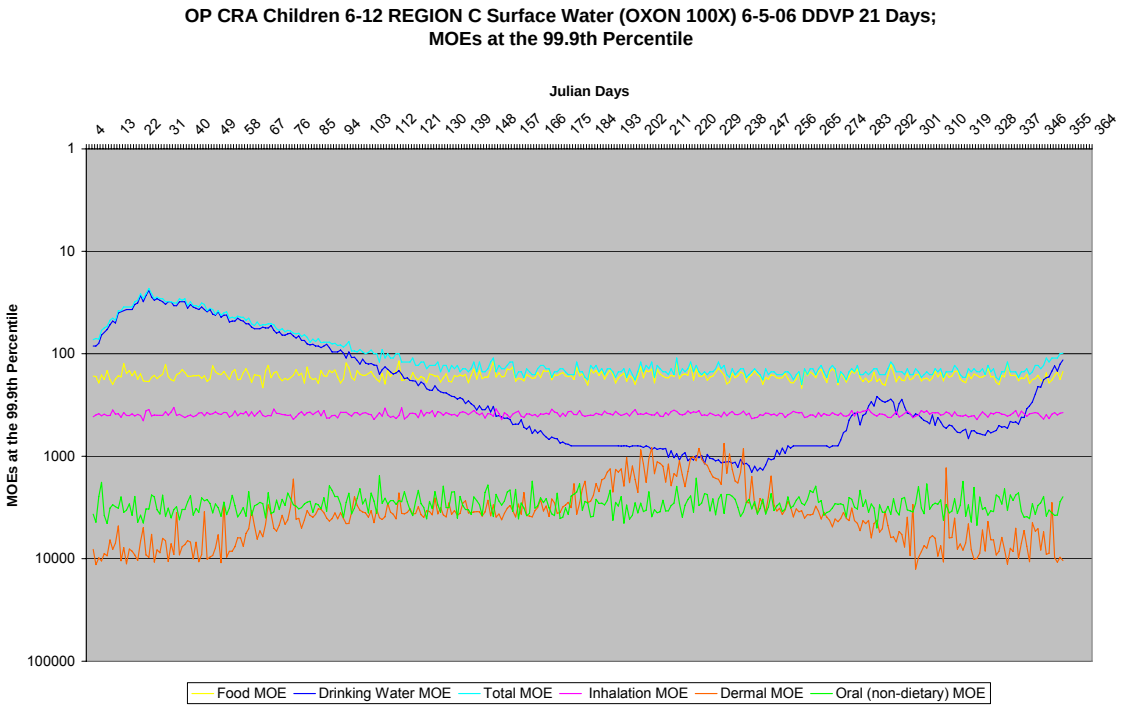

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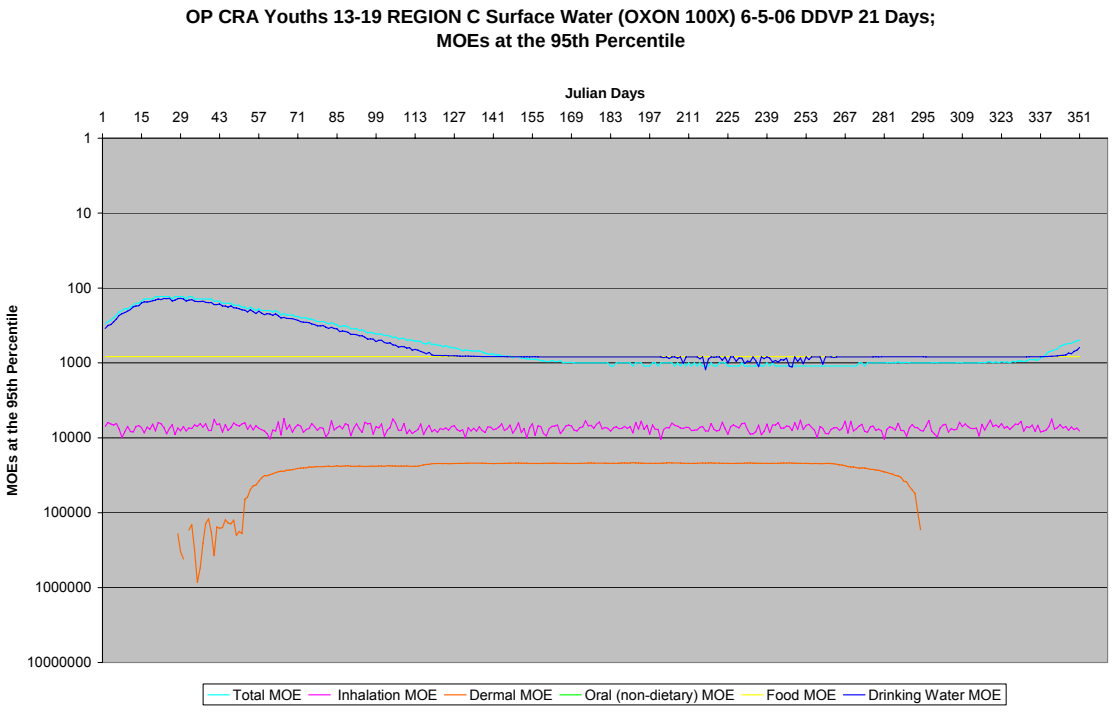

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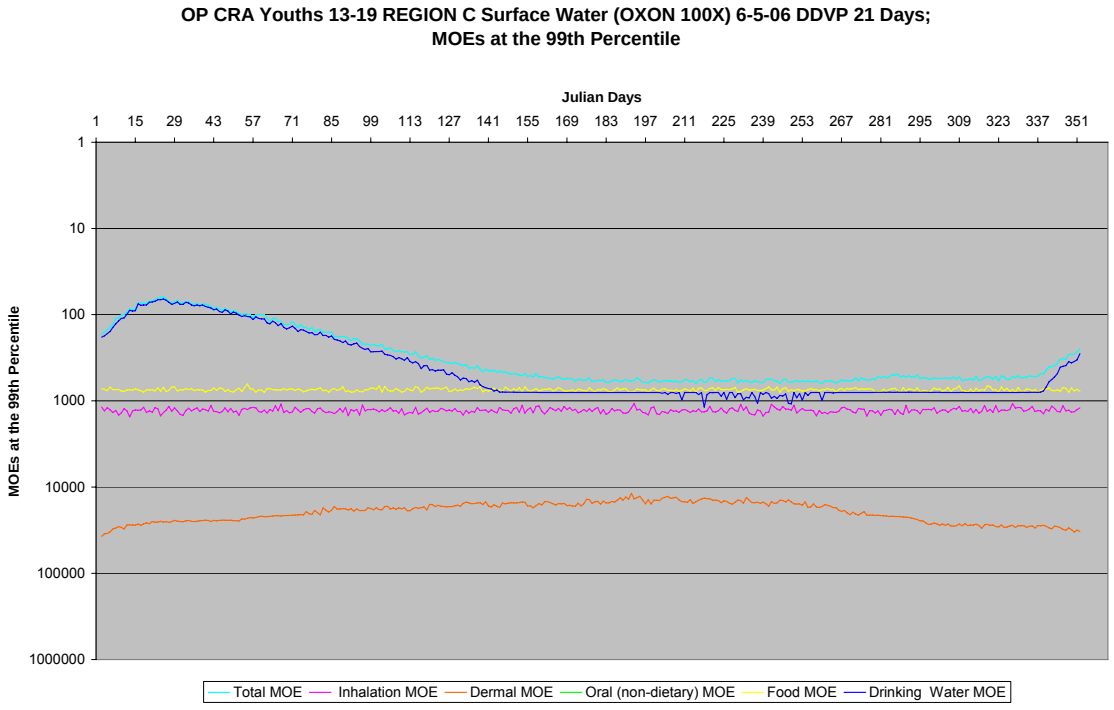

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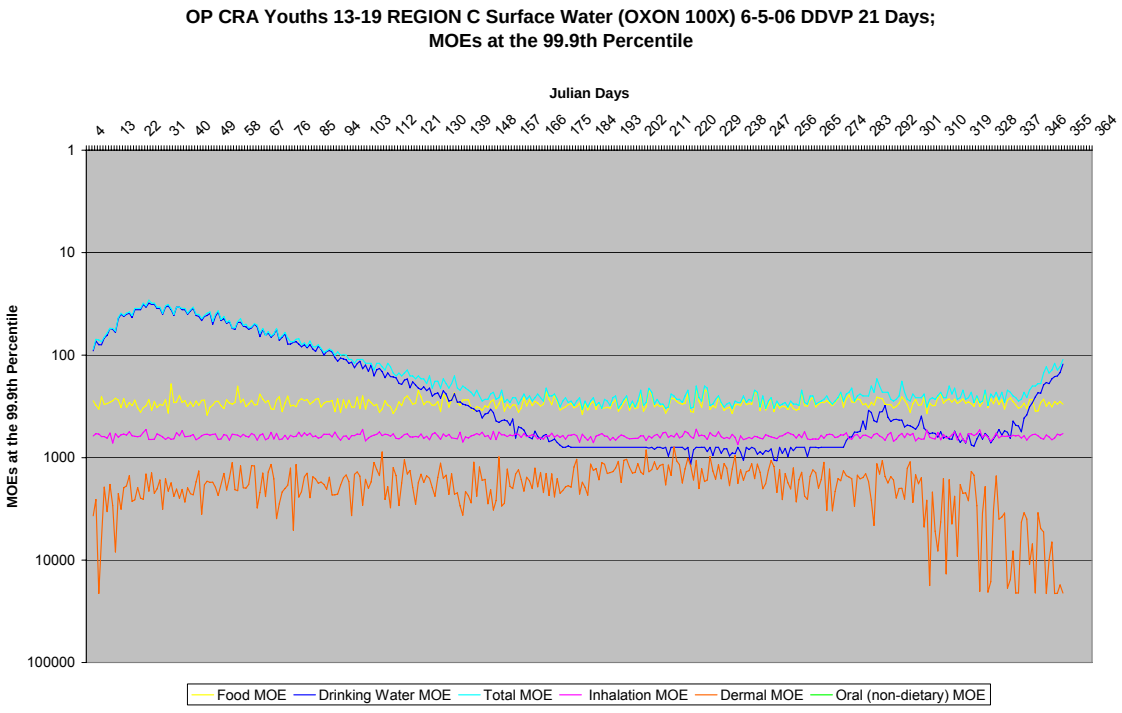


Figure III.D 16

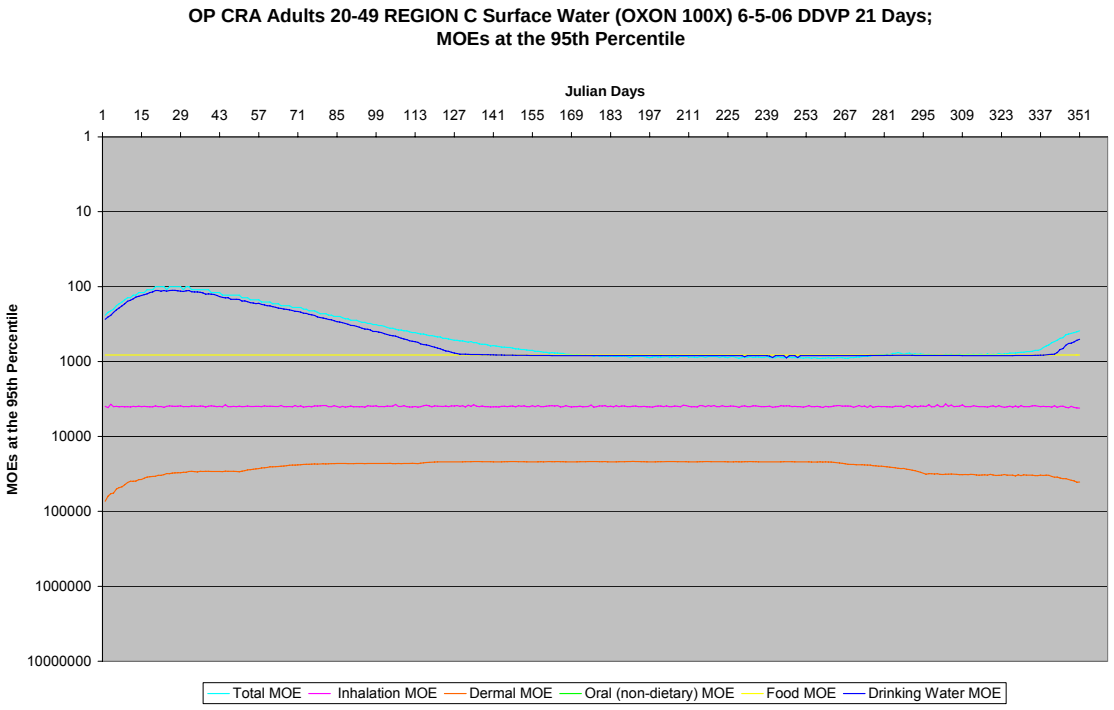


Figure III.D 17

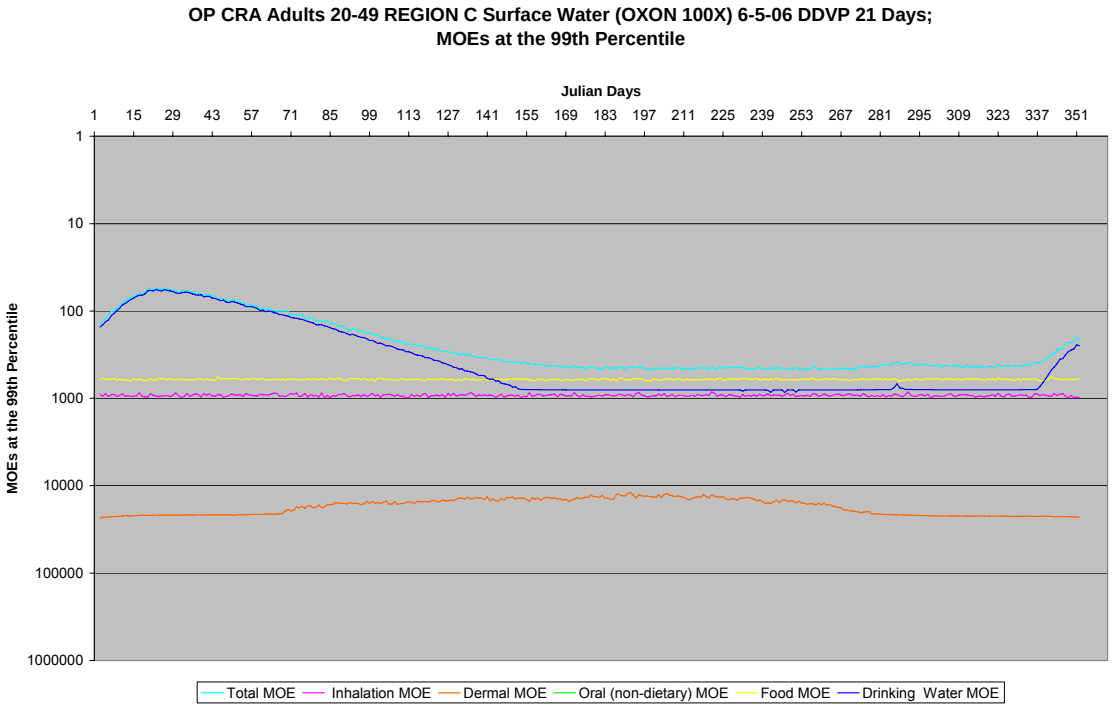


Figure III.D 18

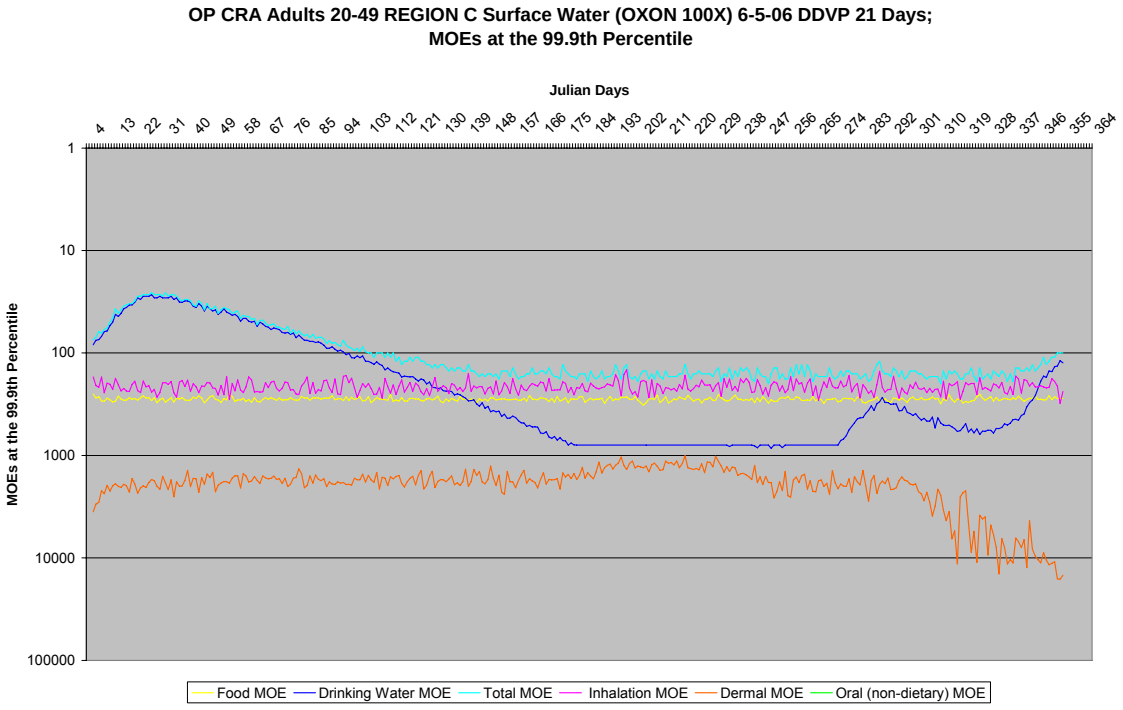


Figure III.D 19

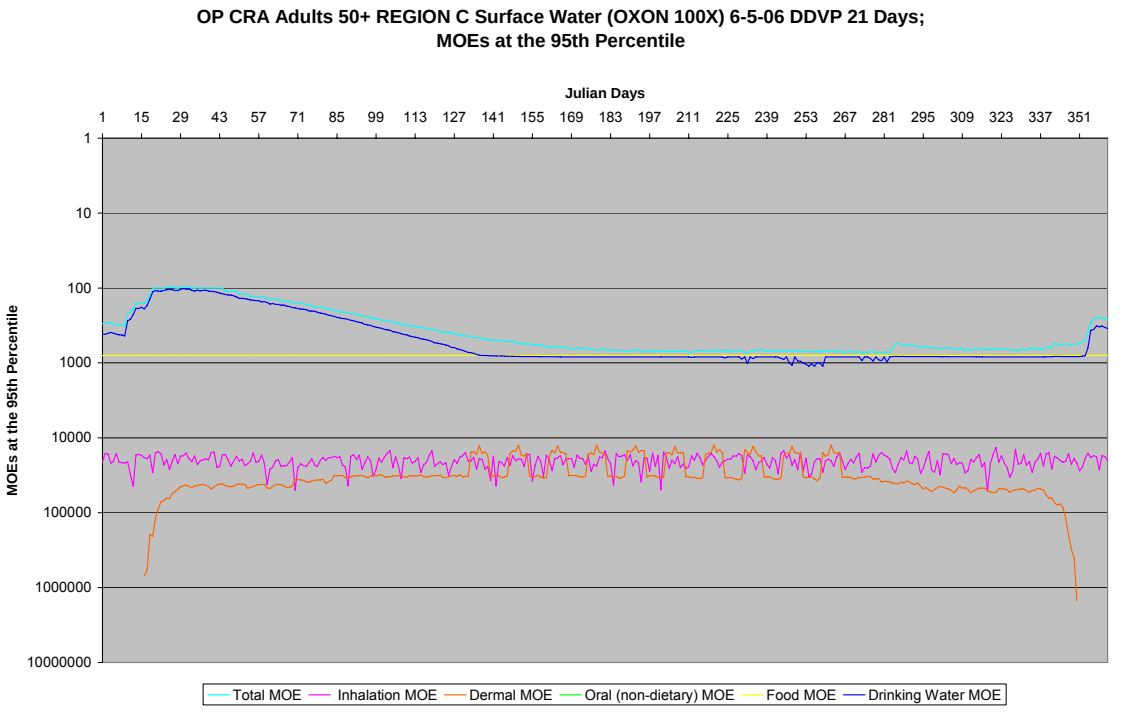


Figure III.D 20

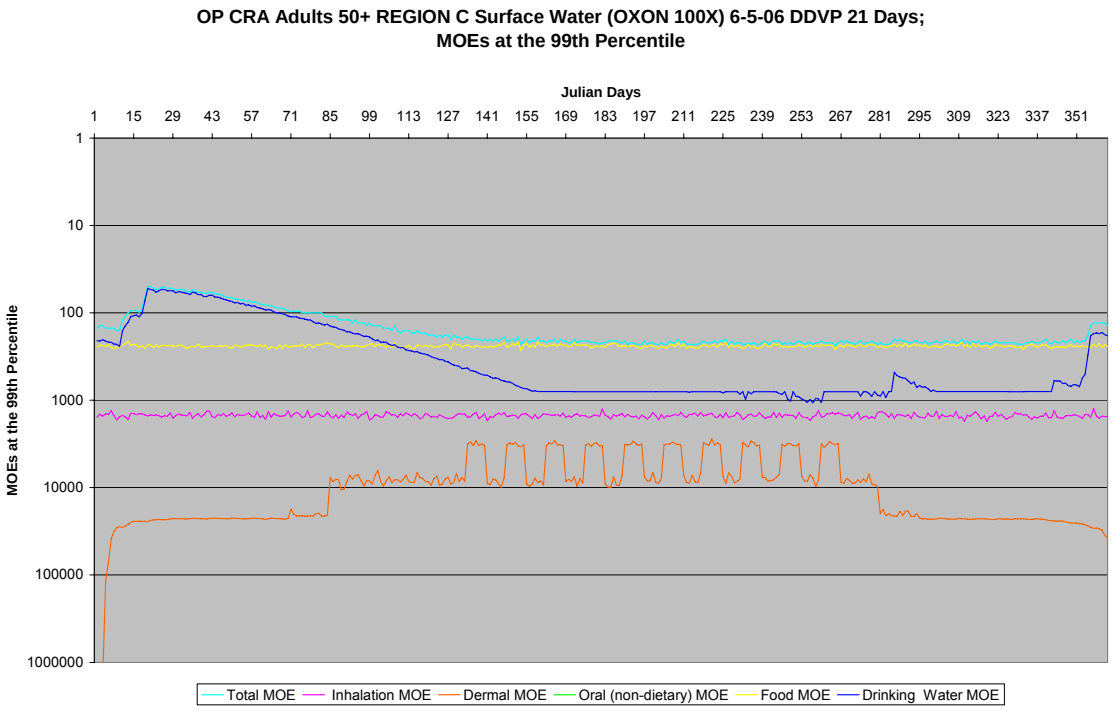


Figure III.D 21

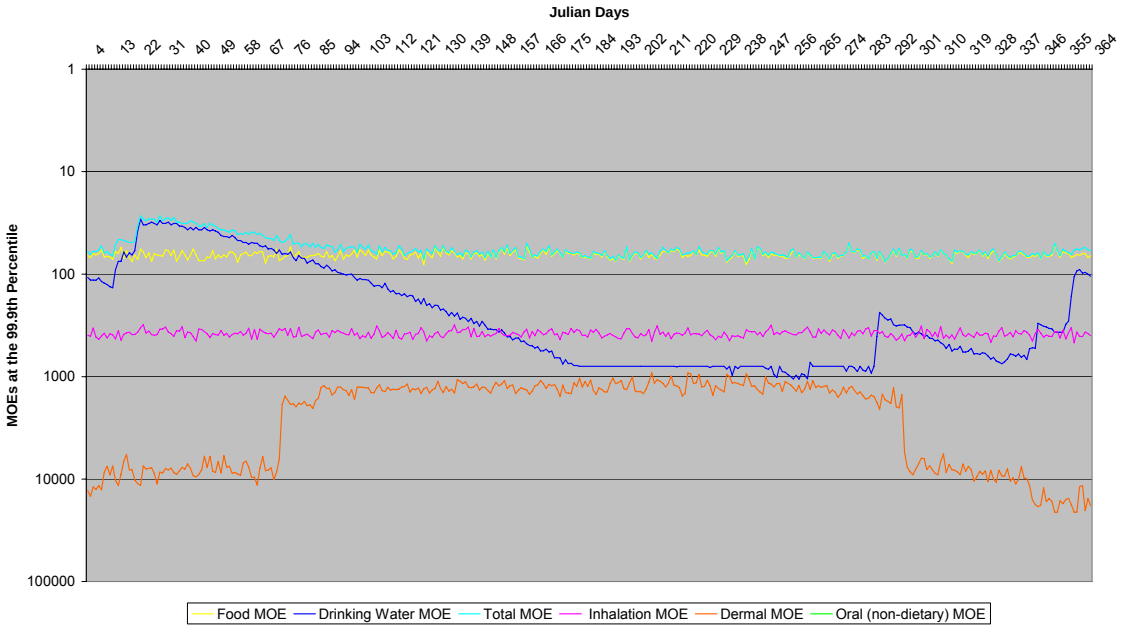


Figure III.D 22

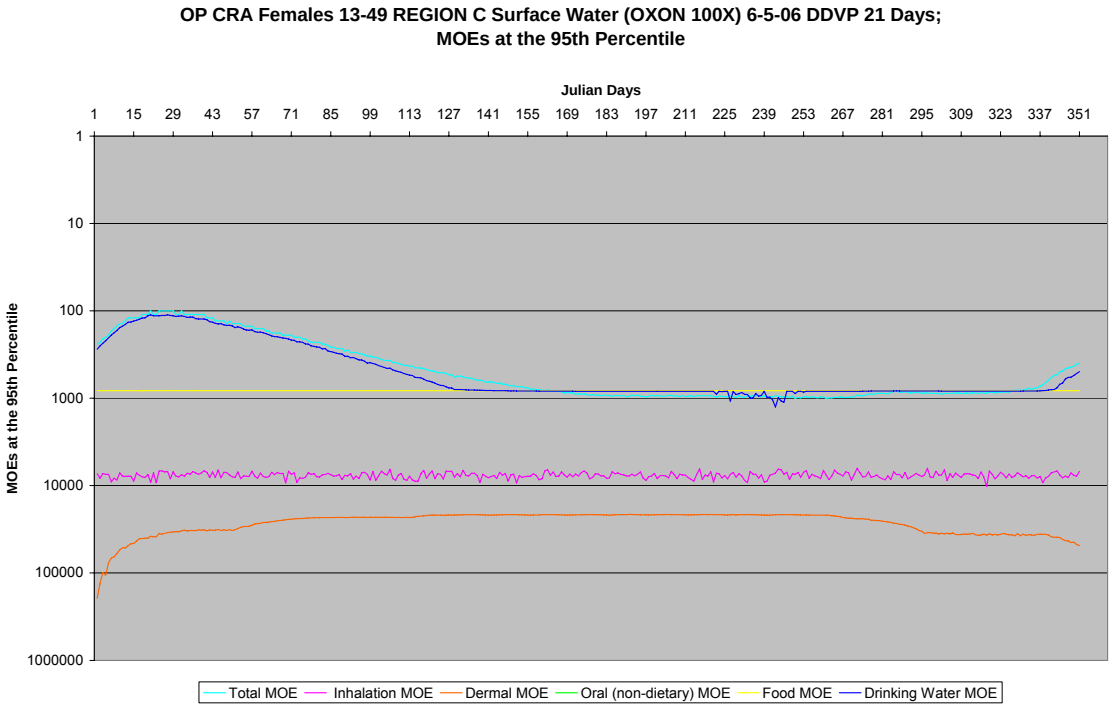


Figure III.D 23

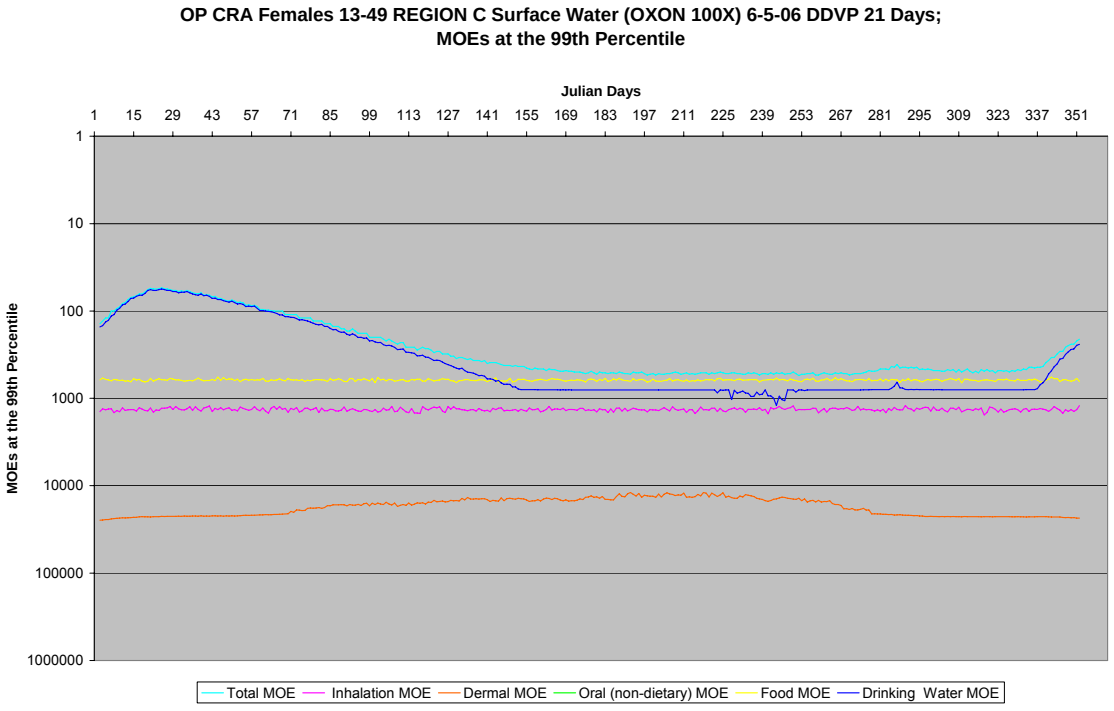
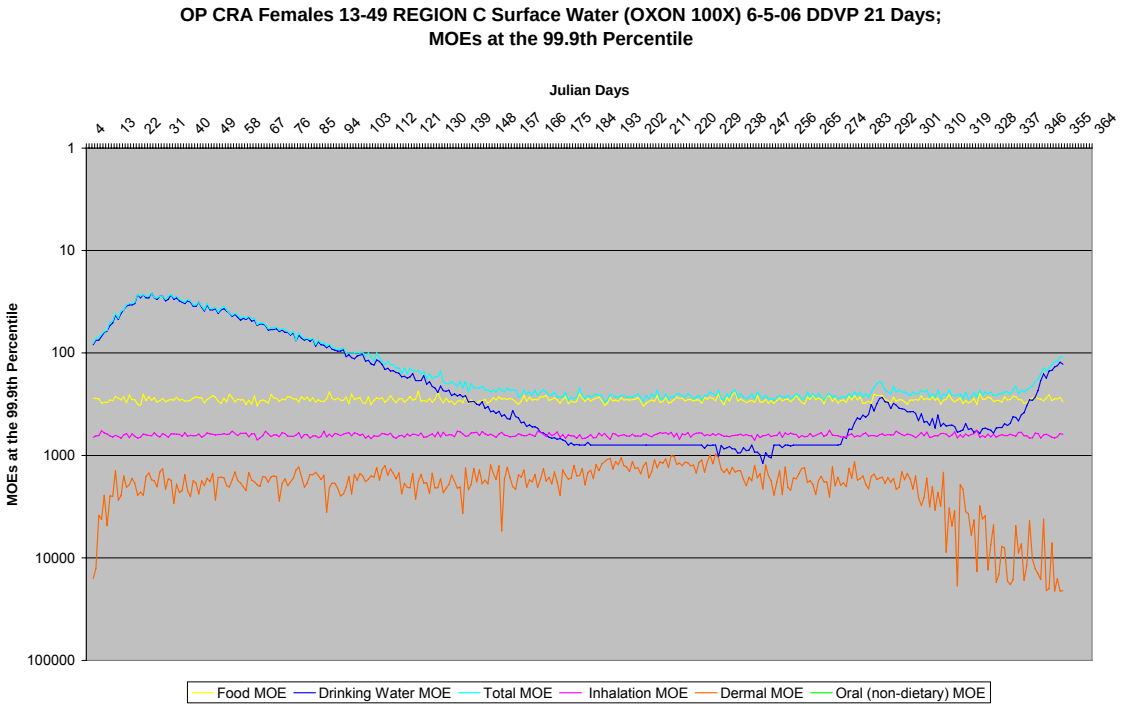


Figure III.D 24



E. Region G

Figure III.E 1

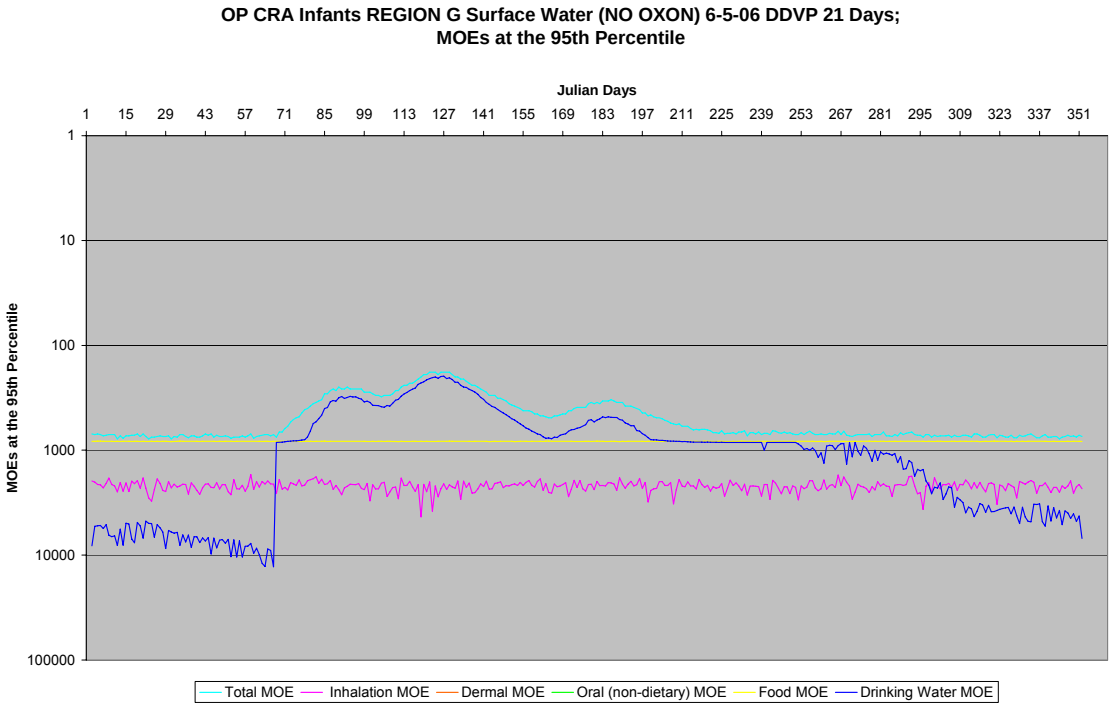


Figure III.E 2

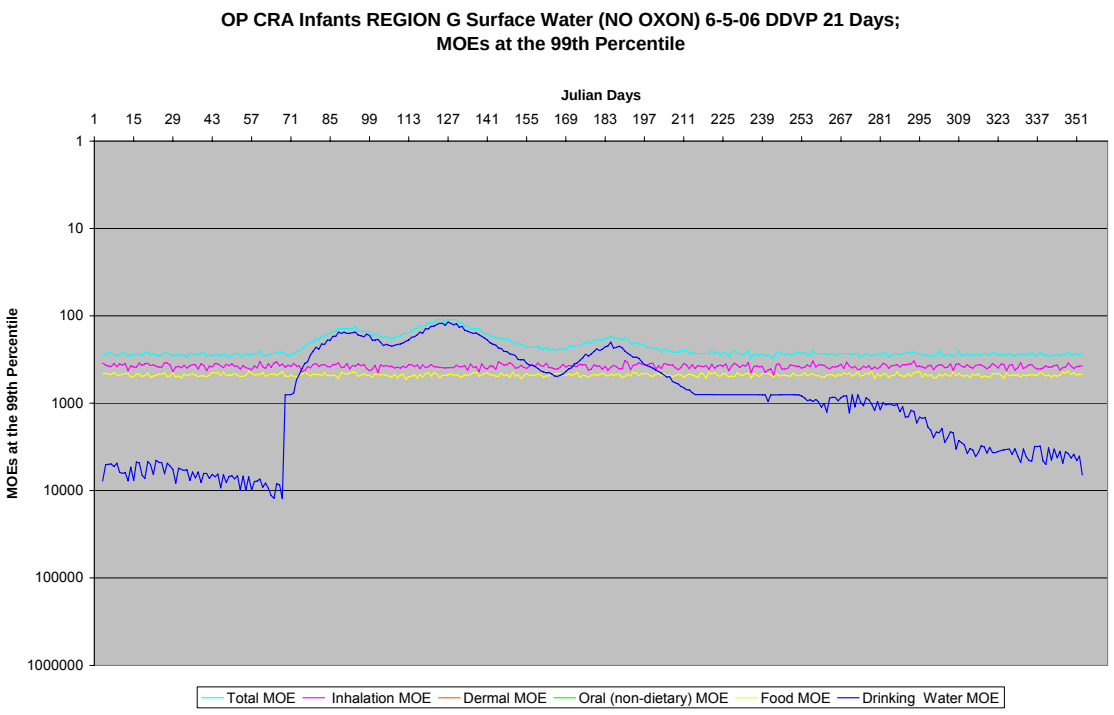


Figure III.E 3

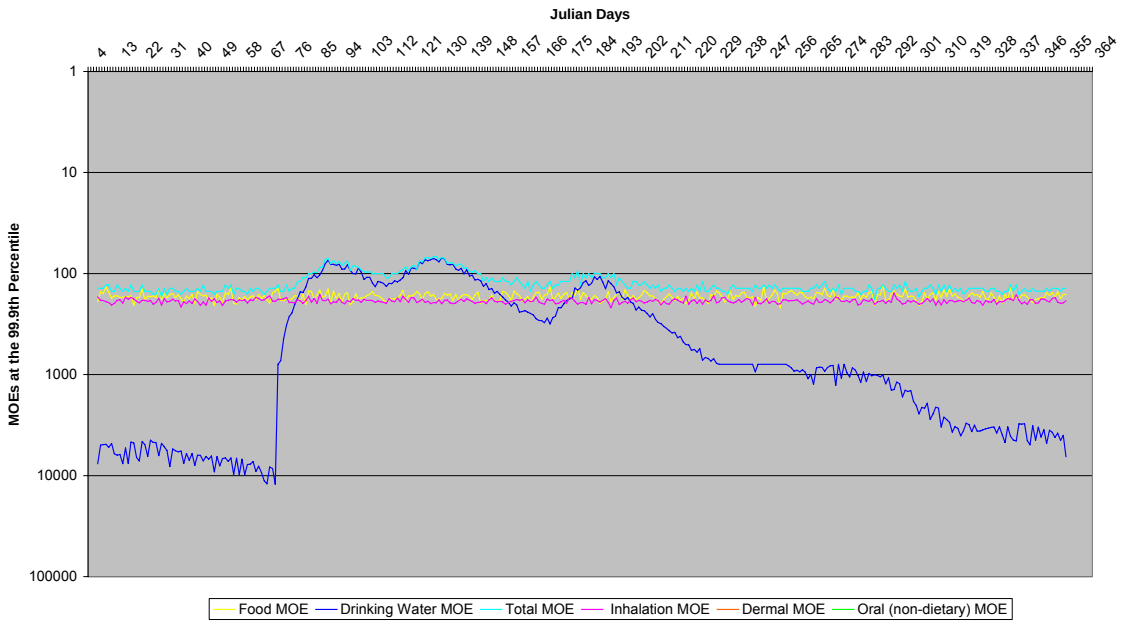


Figure III.E 4

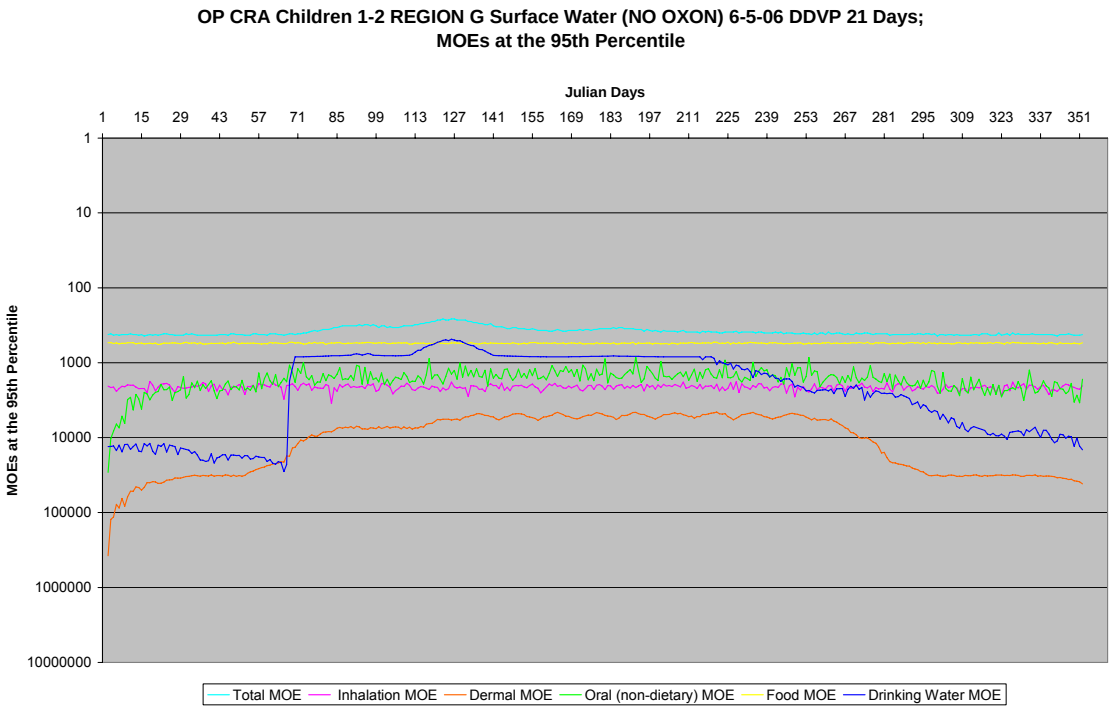


Figure III.E 5

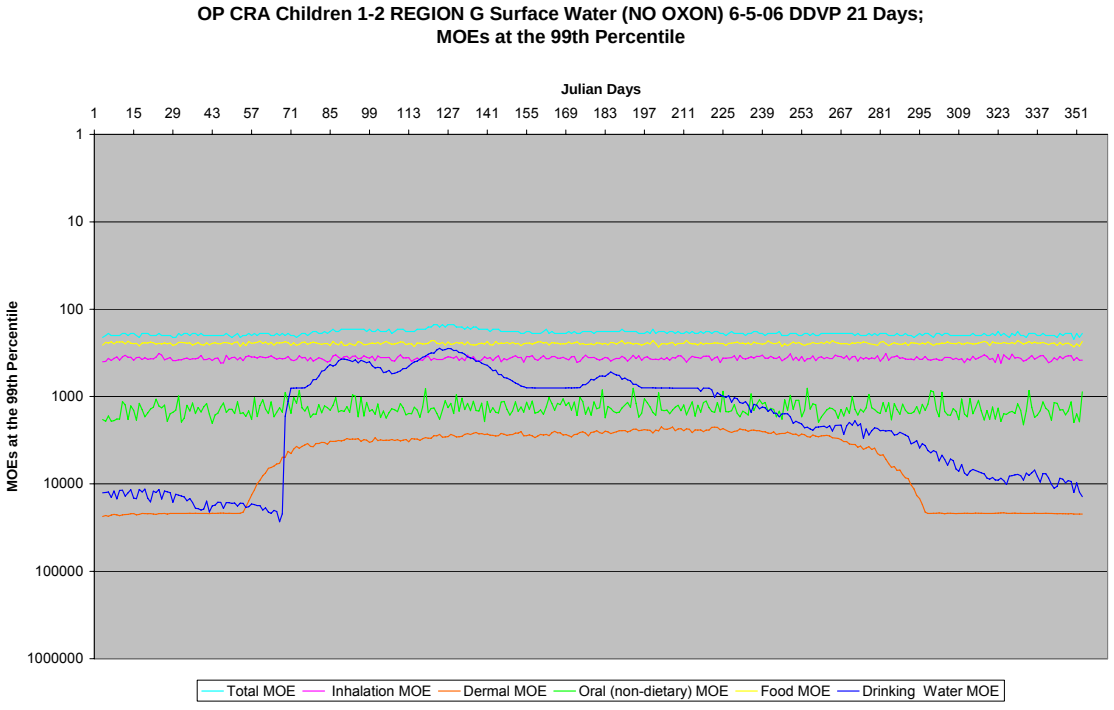


Figure III.E 6

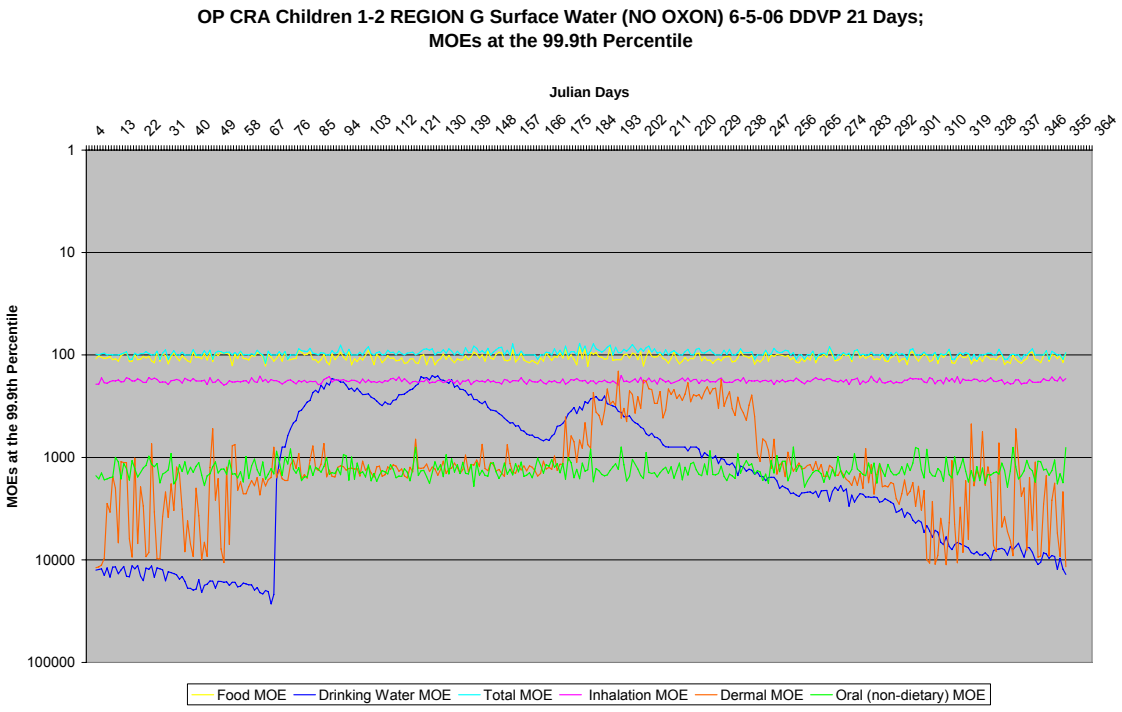


Figure III.E 7

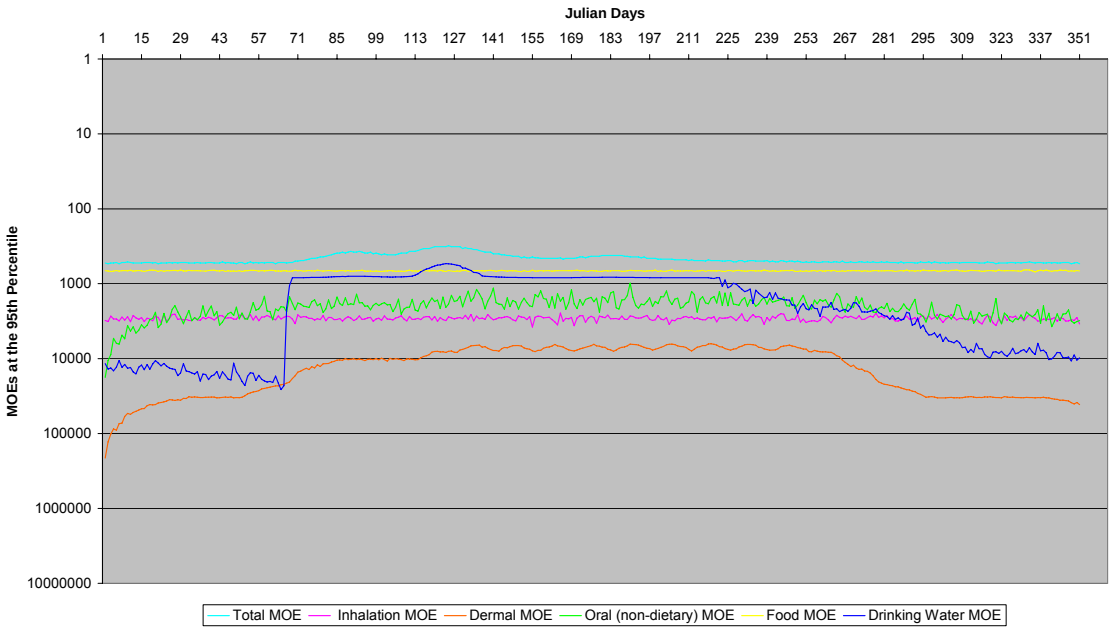


Figure III.E 8

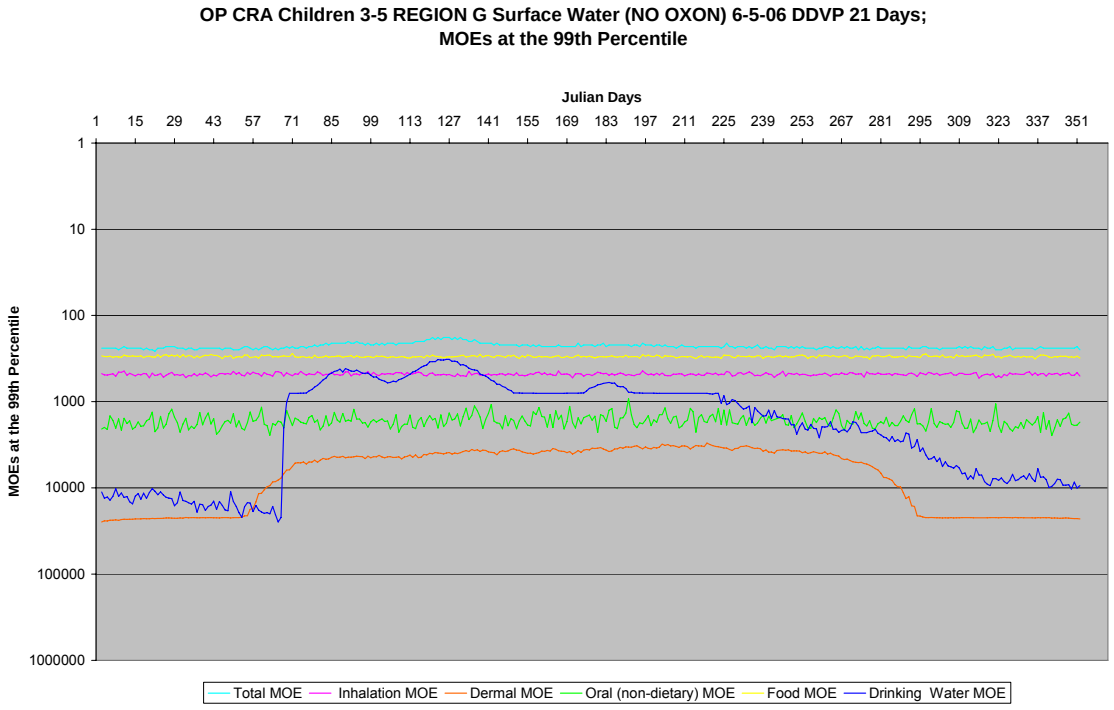


Figure III.E 9

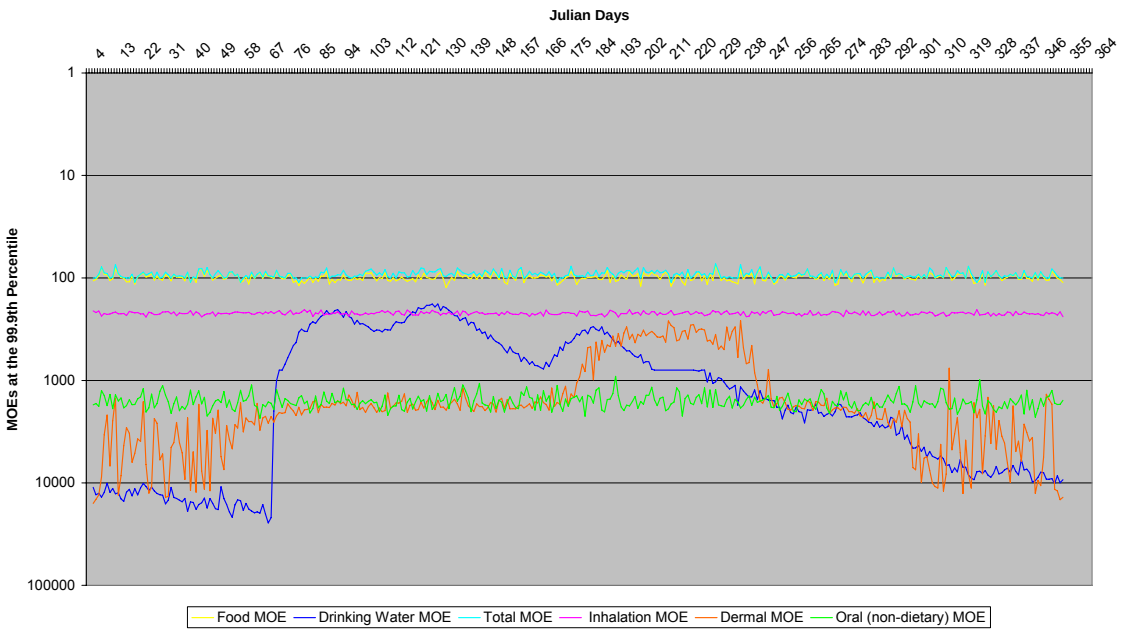


Figure III.E 10

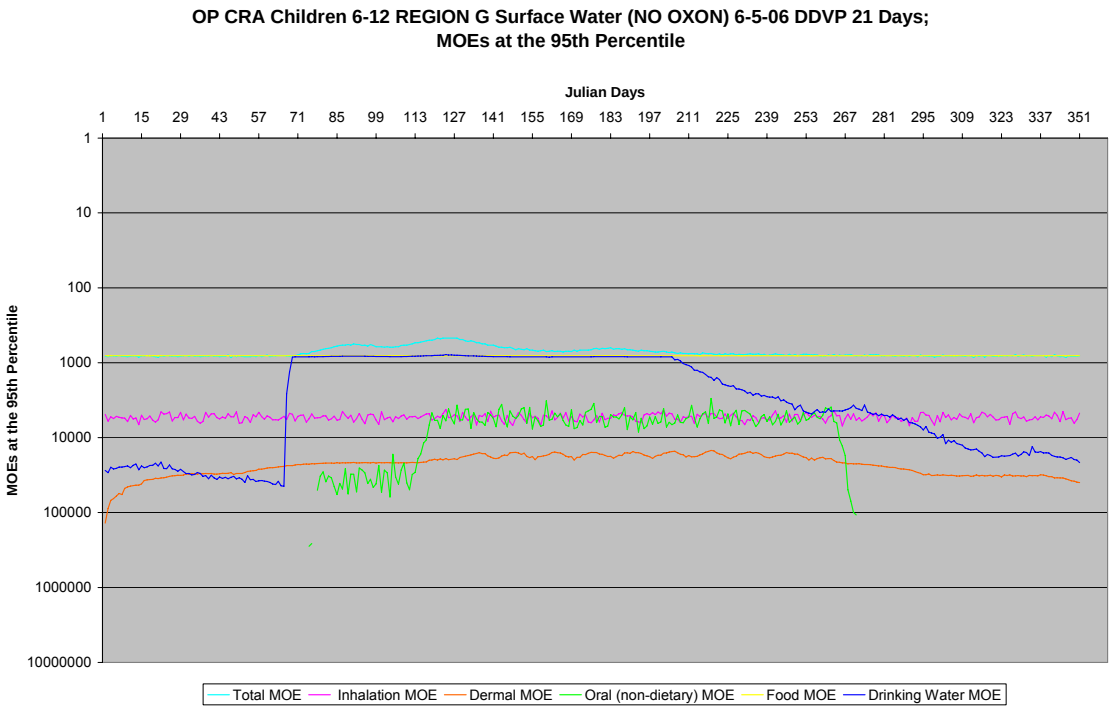


Figure III.E 11

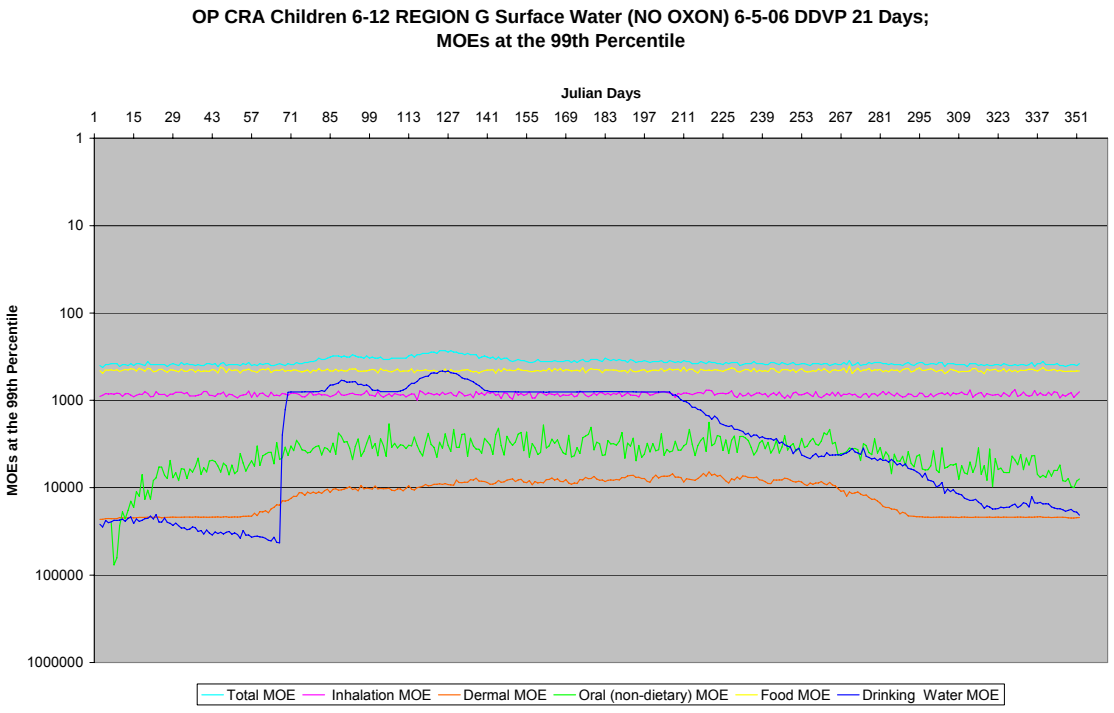


Figure III.E 12

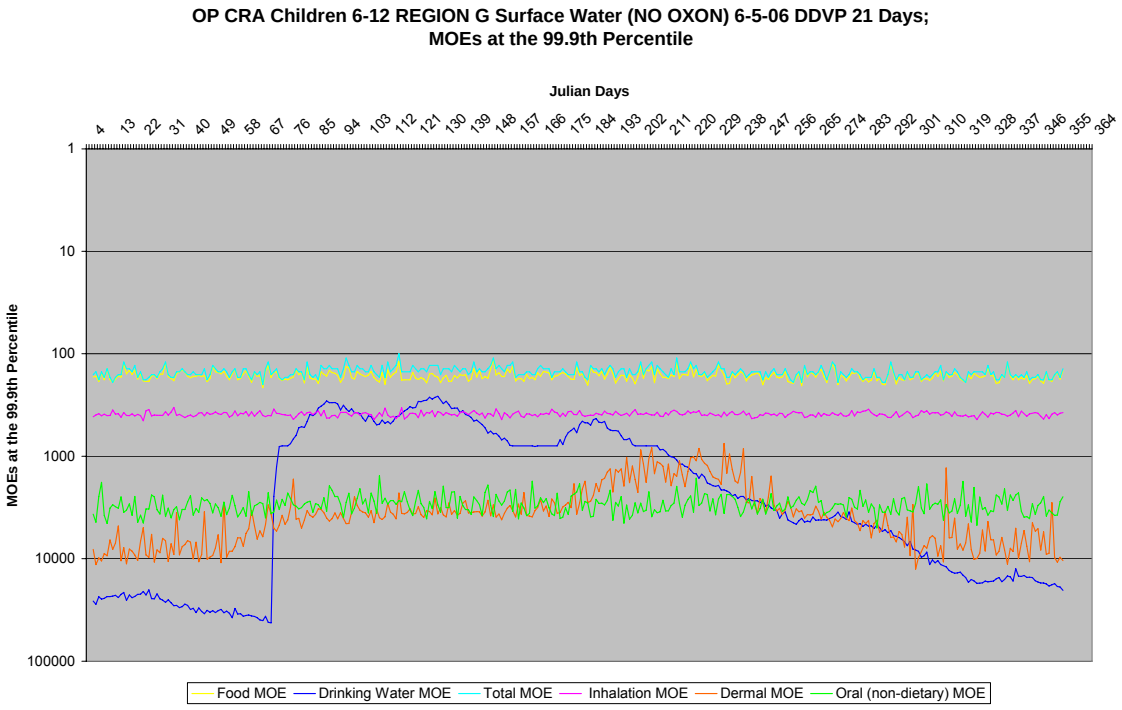


Figure III.E 13

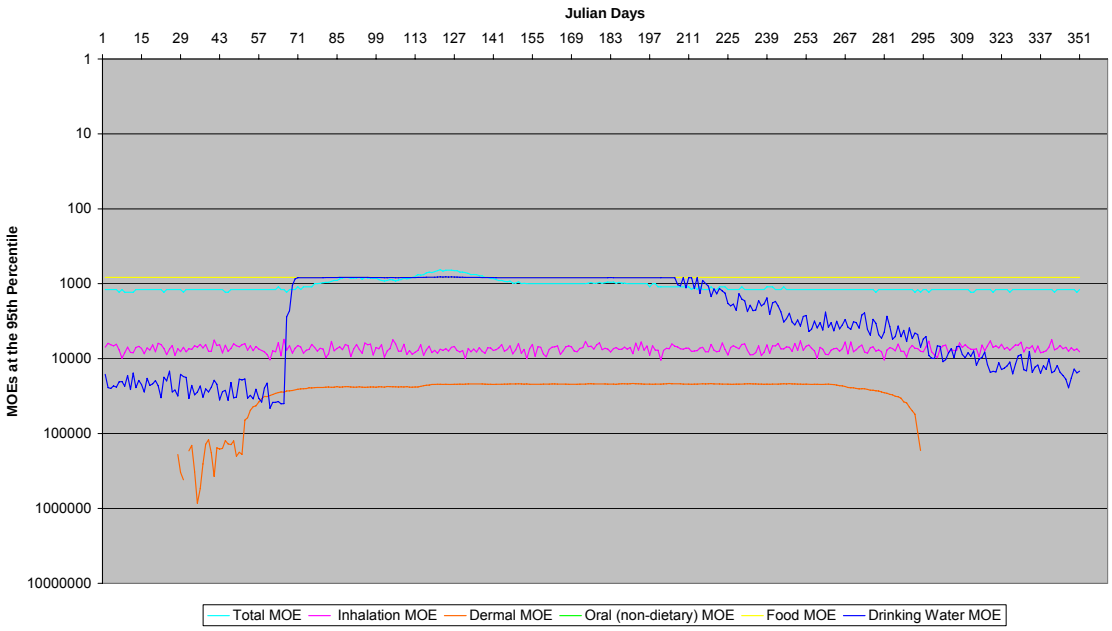


Figure III.E 14

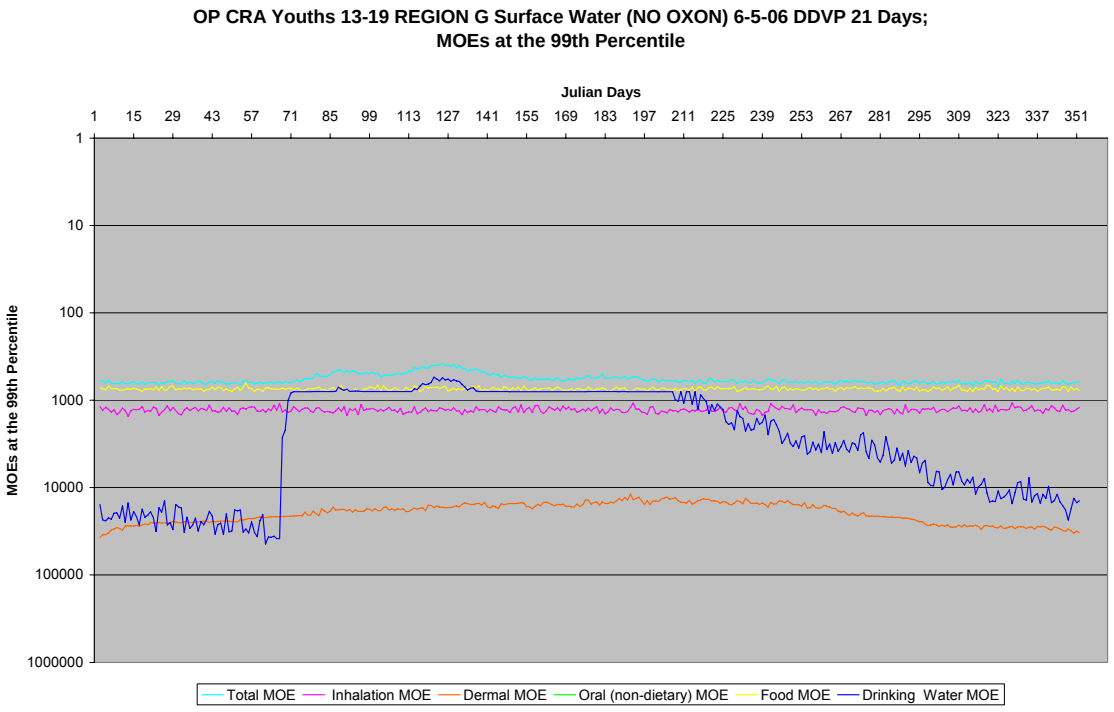


Figure III.E 15

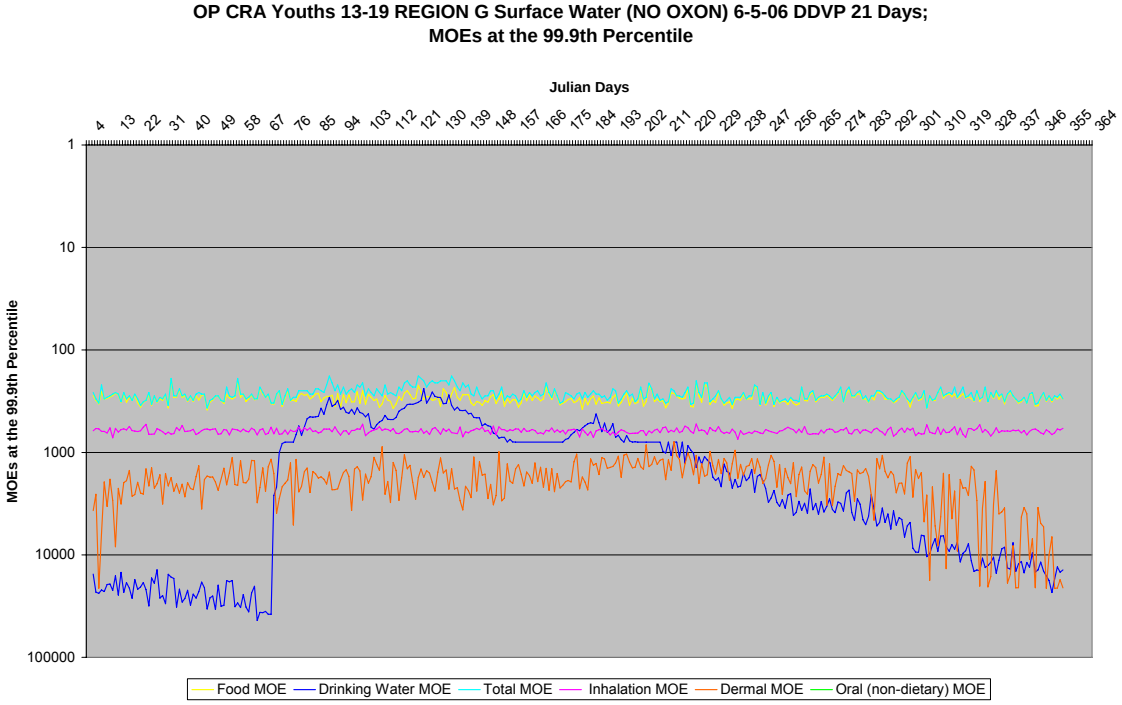


Figure III.E 16

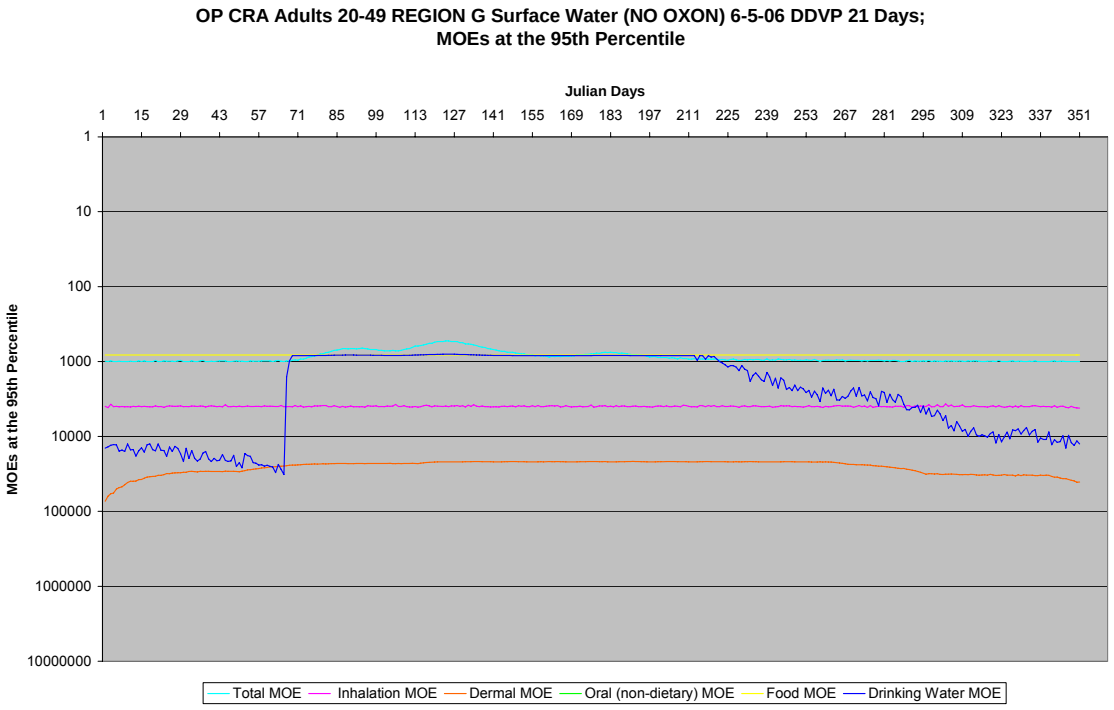


Figure III.E 17

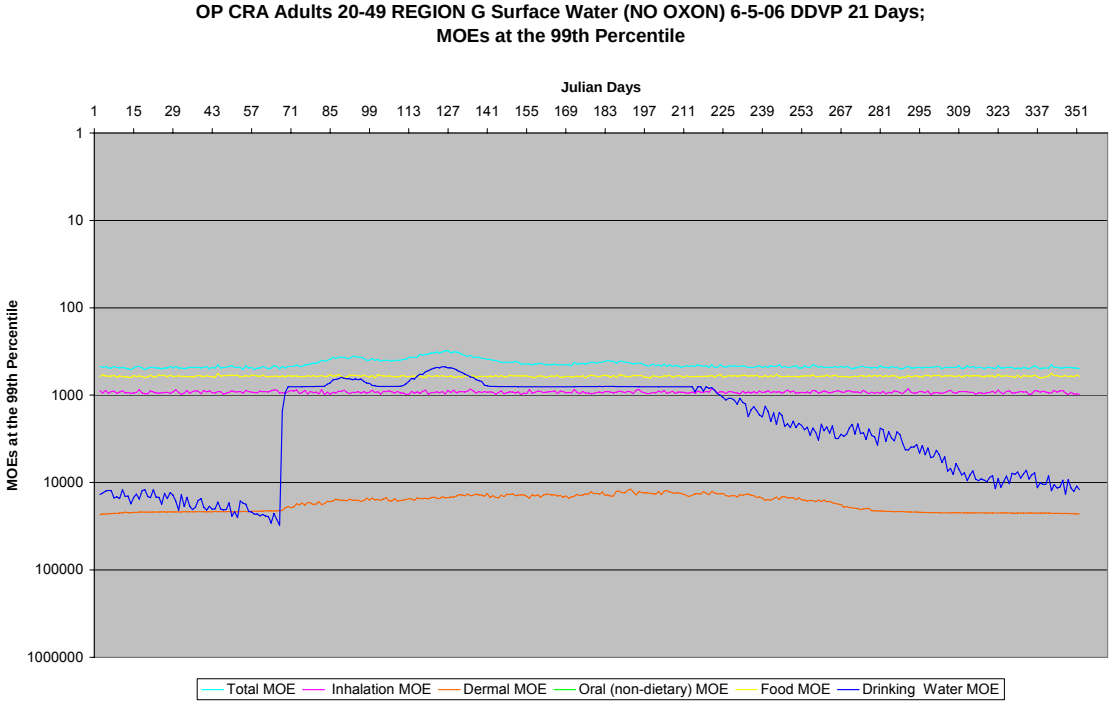


Figure III.E 18

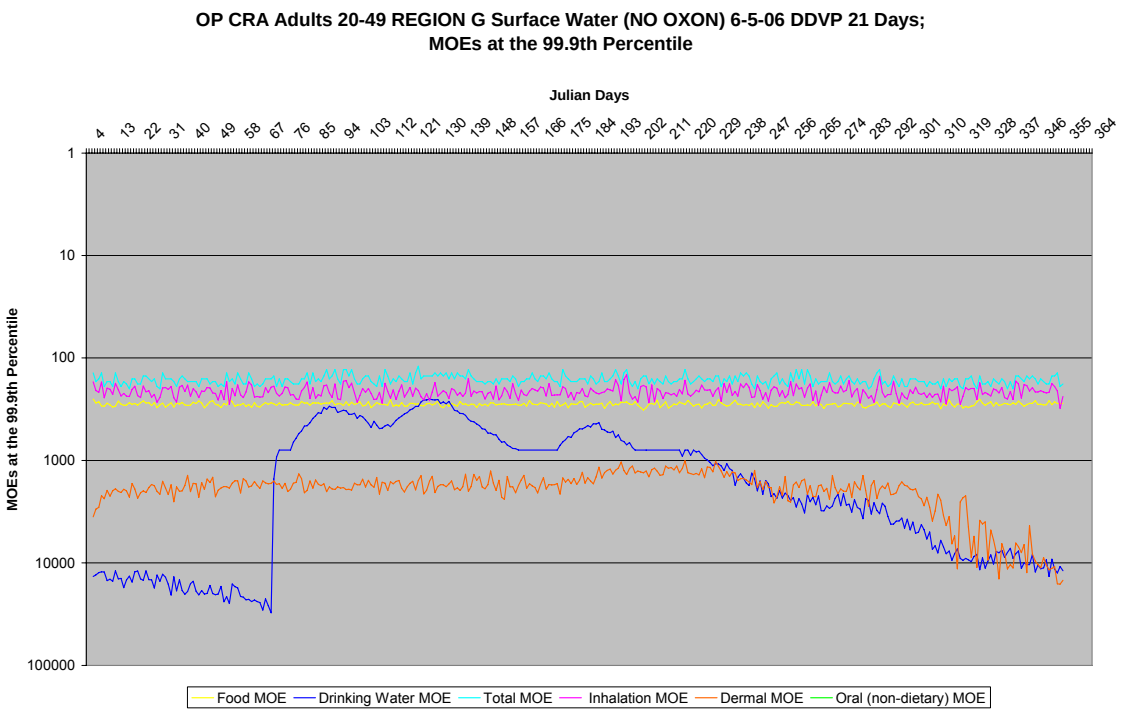


Figure III.E 19

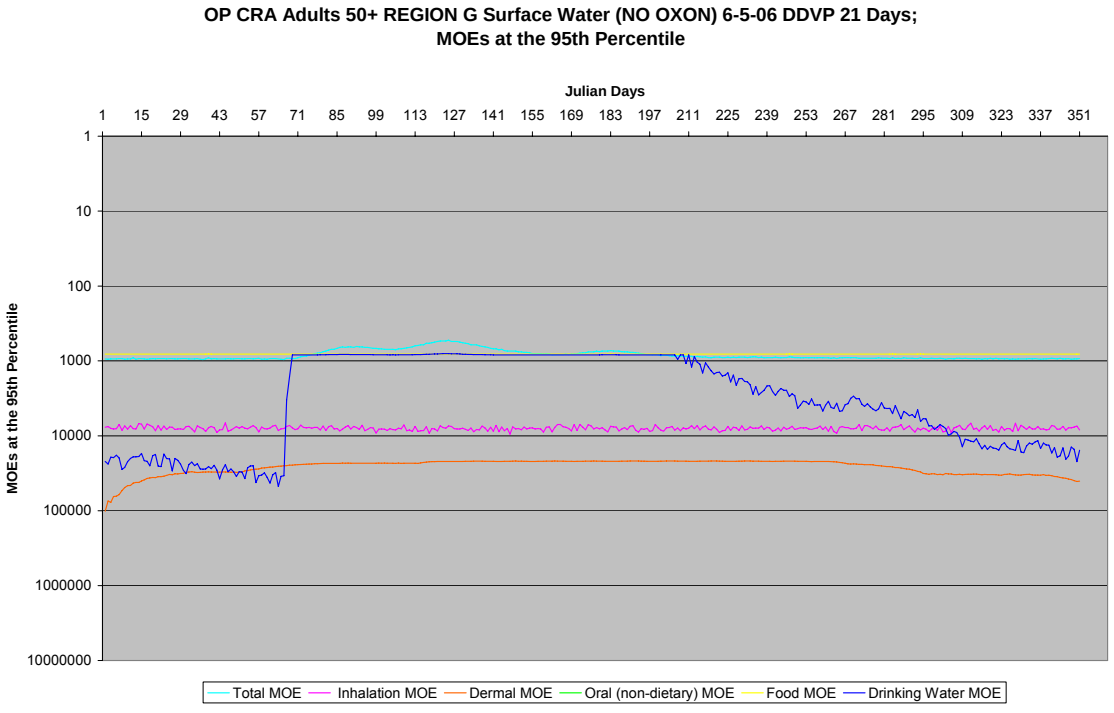


Figure III.E 20

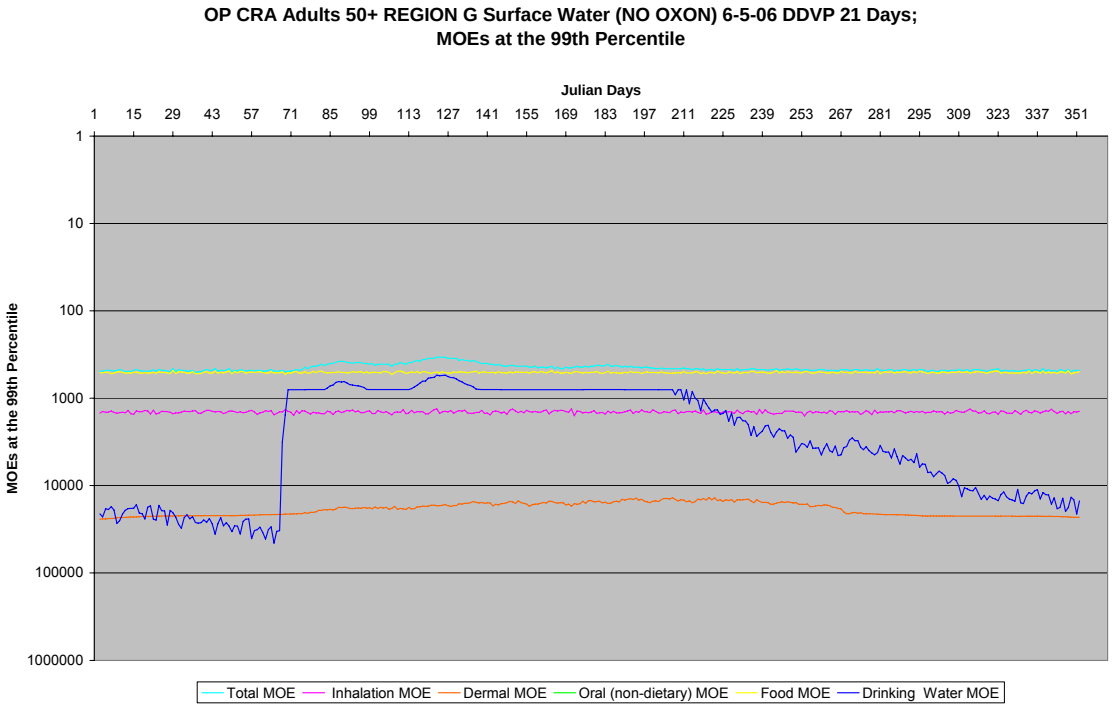


Figure III.E 21

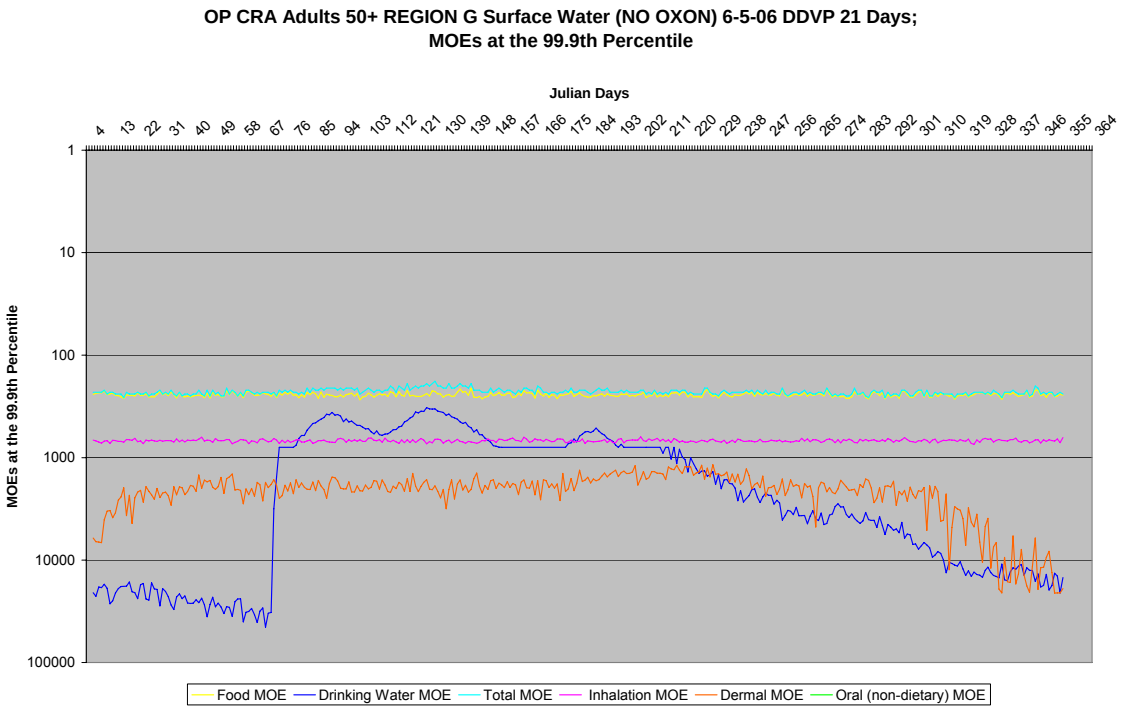


Figure III.E 22

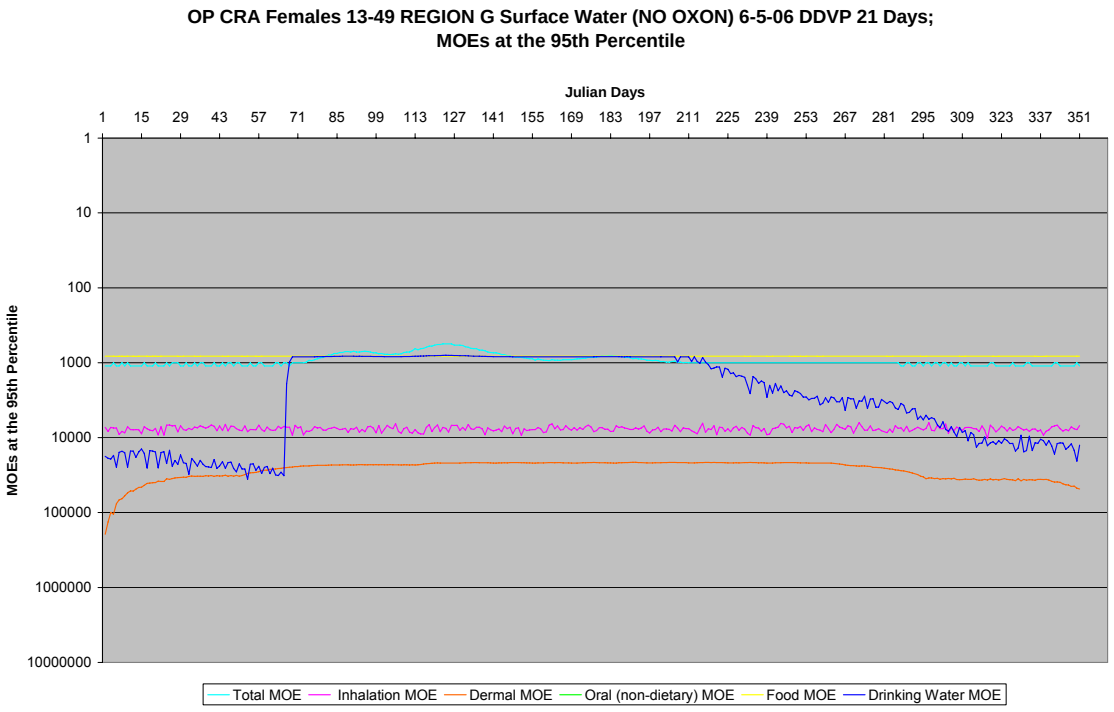


Figure III.E 23

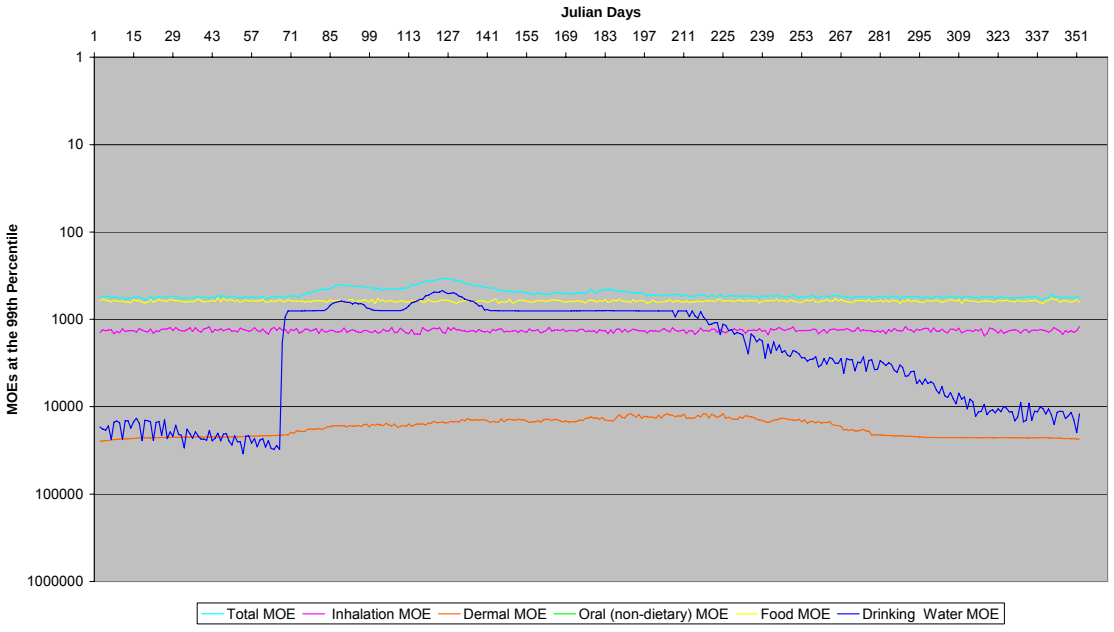


Figure III.E 24