UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
CHEMICAL SAFETY AND
POLLUTION PREVENTION

MEMORANDUM

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SUBJECT: Chlorpyrifos: Preliminary Human Health Risk Assessment for Registration Review

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Background

Attached is the USEPA ("the Agency") Health Effects Division's (HED) preliminary human health risk assessment for the pesticide chlorpyrifos. Chlorpyrifos is a currently being evaluated under the FIFRA section 3(g) registration review program which requires the re-evaluation of pesticides on a 15 year cycle. This preliminary assessment is provided in support of the registration review process for chlorpyrifos.

Chlorpyrifos (O,O-diethyl O-(3,5,6-trichloro-2-pyridyl) phosphorothioate) is an organophosphate (OP) insecticide, acaricide and miticide used to control a variety of insects. Chlorpyrifos was first registered in 1965 for control of foliage and soil-borne insect pests on a variety of food and feed crops. Currently registered uses include food and feed crops, golf course turf, greenhouses, non-structural wood treatments such as utility poles and fence posts, ant bait stations, and as an adult mosquitocide.

In June 2000, during the reregistration process, the Agency released its revised human health risk assessment (D.Smegal, 6/8/00, *Human Health Risk Assessment, Chlorpyrifos*, U.S. EPA). Subsequently, the technical registrants voluntarily cancelled and phased out certain uses of chlorpyrifos. The voluntary cancellation/phase out expeditiously addressed the food, drinking water, residential and non-residential uses posing the greatest risks estimated for children. Risk mitigation measures include eliminating use on tomatoes, restricting use on apples, phasing out termiticide use, canceling all homeowner use product registrations (except insect bait stations), and canceling uses in schools and parks where children may be exposed.

An Interim Reregistration Eligibility Decision (IRED) was issued in February 2002. The IRED included additional mitigation measures addressing occupational and ecological risks not addressed by the 2000voluntary cancellation/phaseout. To mitigate worker risk estimates of concern, a combination of reduced application rates and seasonal maximum limits, increased retreatment intervals, increased PPE and/or use of engineering controls were required as well as increased REIs for a number of crops. Upon completion of EPA's assessment of the cumulative risks from the organophosphate class of pesticides, the chlorpyrifos IRED became final (as a RED) in July 2006.

The June 8, 2000 HED human health risk assessment for chlorpyrifos was largely based on adult laboratory animal data for cholinesterase inhibition and the application of default uncertainty factors, including the retention of the 10x FQPA Safety Factor. Since 2000, there has been extensive and ongoing research on various aspects of chlorpyrifos including its neurological effects in *in vitro* and in animals and humans following gestational and post-natal exposures, and its pharmacokinetics. In 2008, the Agency developed a draft issue paper reviewing the science available for chlorpyrifos which was reviewed by the FIFRA Scientific Advisory Panel (SAP; September 2008). Since the SAP, new studies have been submitted to EPA including a special acute inhalation study, an immunotoxicity study, and acute and repeat dose comparative cholinesterase assays (CCA) in juvenile and adult rats. The CCA studies examined toxicity for both chlorpyrifos and chlorpyrifos oxon. This preliminary hazard characterization and risk assessment for chlorpyrifos includes existing data, findings of new studies made available since the 2000 assessment, and considers comments from the 2008 SAP reviews. This assessment is

considered preliminary and presents risk estimates from both the 2000 assessment (based on toxicity studies using adult animals) and risk estimates based on benchmark dose (BMD) analyses, where appropriate, from sensitive studies which use ages relevant to human exposure. For the final chlorpyrifos human health risk assessment, including determination of the most appropriate toxicological points of departure and FQPA factors, the Agency will consider the weight of the evidence of all available data and take into consideration any comments received.

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1.0 Executive Summary

Use Profile

Chlorpyrifos (0,0-diethyl-0-3,5,6-trichloro -2-pyridyl phosphorothioate) is a broad-spectrum, chlorinated organophosphate (OP) insecticide. Registered use sites include the following: food crops, including fruit and nut trees, many types of fruits and vegetables, and grain crops; and non-food crops such as forage, golf course turf, industrial sites, greenhouse and nursery production, sod farms, and wood products. Public health uses include aerial and ground-based fogger treatments to control mosquitoes. There are currently no homeowner uses except for roach bait products. Permanent tolerances are established (40 CFR§180.342) for the residues of chlorpyrifos in/on a variety of agricultural commodities (including meat, milk, poultry and eggs). There are also tolerances for use in food handling establishments. Chlorpyrifos is manufactured as granular, microencapsulated, soluble concentrate/liquids, water dispersible granular in water soluble packets (WSP) and wettable powder packaged in WSP formulations, as well as impregnated paints, cattle ear tags, insect bait stations and total release foggers. There is a wide range of application rates and methods.

Hazard Identification

The toxicology database for chlorpyrifos is substantially complete (40 CFR 158.340 guideline studies have been submitted) and has been used to characterize toxicity and for selecting points of departure for purposes of the current risk assessment. Chlorpyrifos, like other OPs, binds to and phosphorylates the enzyme, acetylcholinesterase (AChE), in both the central (brain) and peripheral nervous systems leading to accumulation of acetylcholine and, ultimately, to clinical signs of toxicity. In 2000, the Agency concluded for chlorpyrifos that inhibition of cholinesterase (ChE) was the most sensitive effect in all of the animal species evaluated (rats, mice, rabbits dogs) and in humans, regardless of exposure duration. The Agency is maintaining at this time, based on available data, that cholinesterase inhibition (ChEI) provides the most sensitive dose-response information for deriving points of departure for chlorpyrifos. In animals, significant inhibition of plasma and red blood cell (RBC) ChE occur at doses below those that cause brain ChE inhibition.

The toxicity database of laboratory animal studies spans multiple routes of exposure (oral, dermal, inhalation), animal species, lifestages and durations. The database consists of studies ranging from a single exposure (acute) to subchronic and chronic toxicity. Guideline studies on developmental toxicity and specifically developmental neurotoxicity toxicity, and reproductive toxicity. The metabolism and pharmacokinetics of chlorpyrifos is well-characterized due to a variety of studies in different species and lifestages. Recently, a comparative cholinesterase assay (CCA) was submitted which provides information on comparative sensitivity in adult and juvenile rats from acute and repeated exposures to both chlorpyrifos and its oxon. Special studies have been submitted including an acute neurotoxic esterase rat study, cognitive rat study, and recently an acute inhalation study. Chlorpyrifos is not likely to be carcinogenic to humans, based on the lack of evidence of carcinogenicity in studies in rats and mice and the absence of a mutagenicity concern. There was no sign of immunotoxicity in the guideline study at the highest dose tested.

In addition to the extensive body of data on cholinesterase inhibition, there is a growing body of literature with laboratory animals (rats and mice) indicating that gestational and/or early postnatal exposure to chlorpyrifos may cause persistent behavioral effects into adulthood. There are supporting concurrent changes in brain neurochemistry based on both *in vivo* and *in vitro* studies that may underlie these behavioral changes into adulthood. These behavioral effects are seen at doses that typically result in inhibition of ChE *in vivo*. Although there are several biological plausible hypotheses being investigated by researchers, the mode/mechanisms of action resulting in such effects are not known at this time.

In addition, there are three major epidemiology cohort studies evaluating pre- and post-natal pesticide (chlorpyrifos or OPs) exposure in mother-infant pairs with birth outcomes, and childhood neurobehavioral and neurodevelopment outcomes in neonates, infants, and young children. Although there are challenges in interpreting these studies in the context of human health risk assessment, there is consistency across the animal behavior and epidemiology studies, such as delays in cognitive achievement, motor control, social behavior, and intelligence measures. Because ChE inhibition provides the most sensitive dose-response data available, the Agency has focused the preliminary risk assessment on this effect.

Chlorpyrifos has been issued an order to conduct Tier 1 screening phase of the Endocrine Disruption Screening Program.

Points of Departure and FQPA Safety Factor

The focus of the 2011 preliminary risk assessment is on the cholinesterase inhibiting potential of chlorpyrifos. Consistent with this focus, EPA has evaluated the extensive database of ChE data for multiple lifestages and has selected the most sensitive studies which use ages relevant to human exposure. The toxicological points of departure (PoDs) are based on the results of benchmark dose (BMD) analyses where appropriate, and weight of the evidence (WOE) consideration of all reliable data. There are no residual uncertainties in the exposure database. The dietary risk assessment is conservative and is not expected to underestimate dietary exposure to chlorpyrifos and chlorpyrifos oxon.

Similar to risk assessments conducted for other ChE-inhibiting pesticides, juvenile pups aged PND11 provide the sensitive lifestage and endpoint (RBC ChE inhibition) for the acute dietary PoDs of both chlorpyrifos and the oxon. The chronic dietary PoD for chlorpyrifos is based on RBC ChE inhibition from a repeated dosing study in pregnant rats (developmental neurotoxicity, DNT). The cPOD for chlorpyrifos oxon is based on 11 day repeated exposures in adult female rats (CCA study), which is protective of effects in juvenile pups. The acute and dietary PoDs for both chlorpyrifos and the oxon were derived from benchmark dose analyses.

For the dermal route (all durations) the PoD is based on RBC and plasma ChE inhibition in adult rats (NOAEL =5 mg/kg/day). For acute inhalation the PoD is based on lung ChE inhibition in rats. A NOAEL was not identified. For repeated inhalation, the PoD is based on RBC and plasma ChE inhibition (NOAEL = 287 ug/m^3 or 20 ppb from 2 inhalation studies in rats).

A 1x FQPA safety factor (SF) is being proposed for this preliminary assessment for acute and chronic oral exposure for chlorpyrifos since the PoDs are selected from sensitive endpoints (RBC ChE inhibition) in sensitive lifestages/sexes (juveniles and/or pregnant rats). A 1X FQPA SF is also proposed for all dermal durations and repeated inhalation chlorpyrifos exposures. For acute inhalation exposure, a 10X FQPA database uncertainty factor (UF) is applied to account for LOAEL to NOAEL extrapolation (a NOAEL was not identified in the acute inhalation study). A 1X FQPA SF is also proposed for acute and chronic oral exposure for chlorpyrifos oxon because the PODs are based on the most sensitive age group in the CCA study.

Due to the preliminary nature of this assessment the Agency is presenting assessments reflecting both the retention of the 10X FQPA Safety Factor as in the June 2000 chlorpyrifos risk assessment (USEPA 2000) which was largely based on adult animal data, and a preliminary proposal to reduce the FQPA SF to 1X based on more recently available ChE toxicity studies and analyses. Given the focus of this preliminary assessment on ChE inhibition, the Agency believes the ChE data support reduction of the FQPA SF to 1x for most exposure scenarios. EPA is conducting ongoing analyses of newly published literature studies on a variety of challenging scientific issues such as response relationships among different endpoints at lower exposures, animal to human extrapolation, lifestage dependent toxicities, evaluation of the non-cholinergic effects, inter-individual variation, and interpretation of epidemiology studies in the context of the entire database for assessing human health risk to chlorpyrifos. EPA will continue to evaluate all the data/studies to determine the most appropriate FQPA SF in the revised risk assessment and to determine if the new PoDs based on ChE inhibition are adequately protective of neurodevelopmental effects. This final determination will also consider the 2008 SAP comments and the public comments received on this preliminary risk assessment.

Total Uncertainty Factors for Preliminary Assessment:

A total uncertainty factor of 100X was applied to the chlorpyrifos endpoints selected for the acute and chronic dietary, and incidental oral exposures [10X for interspecies extrapolation, 10X for intraspecies variation and a proposed 1X FQPA factor based on a sensitive lifestage and endpoint selected]. Similarly, a total uncertainty factor of 100X was applied to the chlorpyrifos oxon endpoints selected for the acute and chronic dietary exposures to the oxon.

For dermal exposures a total uncertainty factor of 100X was applied [10X for interspecies extrapolation, 10X for intraspecies variation and a proposed 1X FQPA factor].

For acute inhalation exposures, a total uncertainty factor of 300X was applied [3X for interspecies extrapolation, 10X for intraspecies variation and a 10X FQPA database uncertainty factor (for extrapolation from a LOAEL to a NOAEL). The interspecies extrapolation is reduced from 10X to 3X because the RfC methodology for inhalation is used to determine an HEC (human equivalent concentration) and takes into consideration the pharmacokinetic differences between animals and humans.

For short-term and intermediate- term inhalation exposures a total uncertainty factor of 30X was applied [3X for interspecies extrapolation (reduced from 10X because RfC/HEC methodology

used), 10X for intraspecies variation and a 1X FQPA. The repeated inhalation PoDs are considered protective of sensitive lifestages (LOAEL is based on DNT study with pregnant rats).

Exposure/Risk Assessment and Risk Characterization

Dietary

Highly refined acute and chronic dietary (food and water) exposure and risk assessments were conducted for chlorpyrifos. USDA Pesticide Data Program (PDP) monitoring data and percent crop treated estimates were used for most foods. Processing factors from studies were incorporated when available.

The residues of concern for chlorpyrifos in food are for the parent only. Residues of concern in water include both parent chlorpyrifos and chlorpyrifos oxon, a known degradation product of chlorpyrifos. There are limited environmental fate data available for the oxon. The maximum amount of chlorpyrifos transformation to chlorpyrifos oxon (i.e.100%) was used as a conservative assumption based on empirical data that indicate chlorpyrifos quantitatively oxidizes to form chlorpyrifos oxon in a short period of time during water purification and minimal degradation of chlorpyrifos oxon is expected prior to consumption of the treated drinking water. It is possible that some drinking water treatment procedures such as granular activated carbon filtration and water softening may reduce the amount of chlorpyrifos oxon in drinking water; however, it is unlikely that these treatment processes significantly reduce the amount of chlorpyrifos oxon in drinking water. In addition, these treatment methods are not typical practices across the country for surface water. For these reasons, chlorpyrifos oxon is the residue of concern for drinking water.

Environmental Fate and Effects Division (EFED) has provided chlorpyrifos oxon estimated drinking water concentrations (EDWCs) from PRZM-EXAMS modeling for chlorpyrifos use on grapes, corn/soybean and sugar beets in order to provide a range of possible EDWCs representing the many registered chlorpyrifos uses. In general, these grape, corn/soybean and sugar beet uses represent a broad range of higher end, middle, and lower end EDWCs, respectively, modeled for all chlorpyrifos uses. For each of these three crops, the Agency modeled both an average typical application rate, and a maximum application rate. These particular uses were selected as representative crops for this preliminary drinking water assessment because there is a large amount of chlorpyrifos applied to these crops per year, a large portion of these crops are treated with chlorpyrifos, and/or the use locations are distributed throughout the United States.

The EFED drinking water assessment also takes into account non-targeted water monitoring data from the USGS National Water-Quality Assessment Program (NAWQA), USEPA/USGS Pilot Reservoir Monitoring Program, and USDA Pesticide Data Program (PDP) and the California Department of Pesticide Regulation (CDPR). The reported monitoring data concentrations are less than the estimated concentrations derived from modeling recommended for use in the risk assessment. This result is attributed to 1) water monitoring sampling programs do not specifically target chlorpyrifos use areas and may not represent high use areas; therefore, peak concentrations of chlorpyrifos and chlorpyrifos oxon may not be detected, 2) sampling

frequencies in high chlorpyrifos use areas are not designed to capture peak concentrations and 3) there are limited sampling data available for some areas in the United States. Because currently available monitoring data likely underestimates chlorpyrifos and chlorpyrifos oxon concentrations, monitoring data is not an appropriate estimation of the potential exposure resulting from chlorpyrifos use and are not used in this preliminary assessment. (See R. Bohaty, June 2011, D368388 and D389480, *Preliminary Registration Review Chlorpyrifos Drinking Water Assessment* for the complete drinking water characterization.)

For food alone, the preliminary acute dietary risk estimates for all populations assessed were below the level of concern. The most highly exposed subpopulation were children (1-2 years) at 9.0% aPAD.

For water alone (using the chlorpyrifos oxon PoD), the preliminary acute risk estimates using the lower end representative water scenario (sugar beet) were below the level of concern for all populations assessed at the maximum application rate except for infants at 210% aPAD. At the average typical rates for sugar beets, exposures were also of concern for infants (340% aPAD), and children (130-140% cPAD). Using the mid-range representative scenario (corn) the acute risk estimates for all populations assessed were above the level of concern for the maximum application rates; the risk estimate for the most highly exposed subpopulation, infants, was 770% aPAD. However, for typical application rates, the risk estimates were much lower (<120% aPAD) for all populations assessed. Using the higher end representative water scenario (grapes) the acute risk estimates were below the level of concern for all populations assessed at the typical application rates (<59% aPAD for infants), but were above the level of concern at the maximum application rates assessed (2700% aPAD for infants).

The preliminary chronic dietary risk estimates (food alone) for all populations assessed were below the level of concern. The most highly exposed group were children (1-2 years) at 8.4% cPAD [excluding food handling establishment (FHE) uses] and children (1-2 years) at 11% cPAD (including the FHE uses).

For water alone (using the chlorpyrifos oxon PoD), the preliminary chronic risk estimates span a large range, depending on the representative crop and application rate assessed. Using the lower end representative water scenario (sugar beets), risks were below the level of concern for all populations assessed based on the maximum application rates (<69% cPAD) however there were some risks of concern for typical rates assessed for infants and children (110-270% cPAD). Drinking water risk estimates for the mid-range and high end representative water scenarios (corn and grapes), were below the level of concern at the typical application rates (<49% cPAD) for the highest exposed subpopulation, infants (<1 yr), but exceeded the level of concern at the maximum application rates (ranged from 280-890% cPAD) for infants (<1 yr).

Comparison of the Chlorpyrifos Dietary Assessment (June 2000 Assessment and the 2011 Preliminary Assessment)

The acute and chronic PoDs and resulting dietary risk estimates (for the most highly exposed subpopulations only: young children and/or infants) are compared for the June 2000 chlorpyrifos risk assessment and for the current 2011 preliminary assessment.

In 2000 the acute and chronic dietary PoDs were based on NOAELs (plasma and/or RBC ChEI) from oral studies using adult laboratory animals (including pregnant females). The same PoD, based on toxicity of parent chlorpyrifos, was selected for both food and water. A 10x FQPA factor was retained.

For the 2011 preliminary assessment, the acute and chronic PoDs for *food* exposures were based on the toxicity of parent chlorpyrifos (BMDs for RBC ChEI) to juvenile and pregnant animals, respectively. The acute and chronic PoDs for *water* exposures were based on the toxicity of the chlorpyrifos oxon (BMDs for RBC ChEI) from studies where juvenile and adult animals were directly dosed with the oxon. A 1x FQPA factor is proposed.

The acute dietary (food only) risk estimates for the most highly exposed subpopulation were 82% of the aPAD (2000) and 9% of the aPAD (2011).

In 2000 the acute EDWC was not included in the dietary analysis (water residues not incorporated directly into DEEM analysis) and a % aPAD result was not calculated. Instead a Drinking Water Level of Concern (DWLOC) method was used. An estimated ≤18% aPAD value for 2000 water was estimated herein for comparison purposes only and reflects the exposure amount allowed for water in the 'risk cup' after food exposures are subtracted. In the 2011 preliminary water assessment, a range of representative scenarios was assessed (higher end, mid-range, and lower end). The resulting acute drinking water risk estimates (for infants) ranged from 59% to 2700% aPAD, depending on the crop and application rate.

The chronic dietary (food only) risk estimates for the most highly exposed subpopulation were 51% of the cPAD (2000) and 11% of the cPAD (2011).

As in the 2000 acute water assessment, the 2000 chronic water assessment used a DWLOC approach. A ≤ 49% cPAD value was estimated for 2000 water. In the 2011 preliminary water assessment, a range of representative scenarios was assessed (higher end, mid-range, and lower end). The resulting chronic drinking water risk estimates (for infants) ranged from 26% to 890% cPAD, depending on the crop and application rate.

It is important to note that, aside from differences in the PoDs and FQPA factors, there have been changes in the dietary input assumptions since 2000. For example, updated food monitoring data and percent crop treated data were used in the 2011 preliminary assessment. For water, in 2000 EDWCs were based on parent chlorpyrifos and were derived from the SCI-GROW model for groundwater and monitoring data for surface water. It is now believed that the existing water monitoring data are not representative of the potential exposure in drinking water and is not recommended for use in quantitative risk assessment. Groundwater EDWCs are expected to be low relative to surface water based on environmental fate characteristics of chlorpyrifos. Therefore, the SCI-GROW modeling results used in 2000 likely underestimate the potential exposure. The 2011 preliminary risk assessment has used a range of surface water EDWCs derived using PRZM-EXAMS modeling. In 2000 the residue of concern in drinking water was assumed to be parent chlorpyrifos. Empirical data indicate the rapid conversion of chlorpyrifos to chlorpyrifos oxon during typical drinking water treatment; therefore, this preliminary assessment

considers the oxon as the residue of concern in treated drinking water and assumes 100% conversion of chlorpyrifos to oxon. The chlorpyrifos oxon is more toxic than parent chlorpyrifos.

Residential

To date, all homeowner use product registrations have been cancelled, except for roach bait station products, which are not expected to result in residential exposures. Also, applications of chlorpyrifos can be made professionally (not by homeowners) to ant mounds, but residential post-application contact is not anticipated from this use. Additionally, residential/recreational uses remain for aerial and ground-based fogger adult mosquitocide applications and for golf course turf applications, which could result in residential exposures.

Of the residential uses, only the roach bait products can be applied by a homeowner in a residential setting; however, a quantitative exposure/risk assessment for application of the roach bait products was not conducted because HED expects exposure to be negligible. With roach bait stations the active ingredient is completely contained within the bait station. Post-application homeowner exposure from residential ant mound treatment (applied by professionals only) was not quantitatively assessed because contact with the mound is not anticipated. Only residential exposures anticipated from the chlorpyrifos mosquitocide use and golf course use are quantitatively assessed. In addition, a residential bystander exposure has been quantitatively assessed which considers exposure from field volatilization of applied chlorpyrifos.

Estimated short-term adult and child dermal exposures, as well as child incidental oral exposure, to turf following either aerial or ground mosquito treatments do not exceed the level of concern (i.e. calculated Margins of Exposure, or MOEs, are $\geq$ 100). Combined child exposure estimates (dermal and incidental oral) to turf following *aerial* mosquito treatment result in risk estimates of concern; however, combined risk estimates following *ground* treatment are not of concern. Acute adult and child inhalation (spray drift) exposure following *aerial* mosquito treatment results in risk estimates that are not of concern (i.e. MOEs are $\geq$ 30), but risk estimates are of concern following *ground* treatment. Inhalation exposure from ground based ULV treatment was assessed by assuming that the entire active ingredient applied to a 1 acre area is airborne and available to be inhaled by a child or adult.

Adult dermal exposure risk estimates from golfing do not exceed the level of concern (i.e. MOEs are $\geq$ 100) using any of the transferable residue (TTR) region-specific data for the emulsifiable concentrate formulation at the 0.25 and 1.0 lb ai/A application rates.

The Agency has developed a preliminary bystander inhalation exposure assessment for chlorpyrifos using currently available inhalation toxicity and chlorpyrifos air monitoring data. EPA has assessed residential bystander exposure from field volatilization of applied chlorpyrifos based on the available *ambient* and *application site* air monitoring data. Of the 24 acute *ambient* air concentrations assessed, 4 result in risk estimates exceeding the level of concern (i.e. MOEs are < 300). No short-/intermediate-term *ambient* data assessed result in risk estimates of concern (i.e. MOEs are > 30). Of the 5 acute *application site* air concentrations assessed, 3 resulted in a risk estimate of concern (i.e. MOEs are < 300). Of the 5 short- and intermediate-term

application site air concentrations assessed, 4 resulted in risk estimates of concern (i.e. MOEs are < 30).

The bystander exposure assessment is considered preliminary. Some of the limitations identified include the assumption that an individual is exposed to a constant chlorpyrifos concentration in a stationary outdoors location for 24 hours. As part of the December 2009 SAP, the Agency presented their analysis of several models that could be used as screening tools to predict the air concentration and volatilization flux based on intrinsic properties and transport behaviors of pesticides. The Agency is currently in the process of evaluating the SAP's comments. As appropriate, the Agency may revise the modeling approach presented to the SAP may revisit the residential bystander exposure and risk assessment.

Aggregate

A quantitative aggregate (food, water and residential exposures combined) assessment was not performed for this preliminary chlorpyrifos assessment. The preliminary risk estimates for water alone exceed the level of concern and are the primary driver in this assessment. Combining food and/or residential exposures with the water exposures would not be expected to have a significant impact on the resulting risk estimates for water alone. A quantitative aggregate assessment for food, water, and residential exposures will be considered during the final chlorpyrifos risk assessment.

With regard to potential aggregate exposures for workers, the Agency is carefully considering a number of complex science issues, and extensive public comments received on OPP's proposed policy "*Revised Risk Assessment Methods for Workers, Children of Workers in Agricultural Fields and Pesticides with No Food Uses*" (EPA-HQ-OPP-2009-0889-0002).

Occupational

Short- and intermediate-term inhalation and dermal exposure and risk estimates were calculated for occupational handlers of chlorpyrifos for a variety of exposure scenarios at differing levels of personal protection (long-term exposures not expected). The assessments used surrogate data and non-chemical specific exposure studies. In total, 305 exposure scenarios which consist of unique combinations of product formulation, crop or target, application rate, and area treated were assessed.

Of the 305 exposure scenarios assessed 134 had risk estimates that did not exceed the level of concern at some level of personal protection (i.e. calculated Aggregate Risk Estimates, or ARIs, are > 1). Ninety-one (91) exposure scenarios had risk estimates not of concern when engineering controls were considered. The remaining 80 scenarios resulted in risk estimates of concern (i.e. ARIs are < 1) at all levels of personal protection and engineering controls considered.

In an effort to characterize occupational handler risk estimates calculated using both surrogate data and chemical specific biomonitoring (passive dosimetry) data, HED has presented a comparative analysis of these for applicable scenarios. Of the 4 exposure scenarios compared, 3 (mixing/loading liquids for airblast application, airblast applications, and groundboom

applications) resulted in greater risk estimates using biomonitoring data than those estimated using surrogate data (i.e., the estimated MOEs are lower). The analysis of the exposure scenario mixing/loading liquids for aerial application resulted in reduced risk estimates using biomonitoring compared to surrogate data. Because a number of issues were identified which limit the utility of the available biomonitoring data, HED has determined that these data are best suited for characterization of the estimates calculated for representative exposure scenarios using the surrogate data.

Short- and intermediate-term exposure and risk estimates were calculated for occupational handlers performing seed treatment activities in commercial settings and for occupational secondary handlers from planting chlorpyrifos-treated seeds. No chemical-specific handler exposure data were submitted in support of this use pattern.

The majority, 61 of 64, occupational handler seed treatment exposure scenarios assessed (combined dermal and inhalation) resulted in risk estimates which were not of concern (i.e. ARIs are > 1) at some level of personal protection. The remaining 3 exposure scenarios resulted in an ARI < 1 at all level of personal protection considered and, therefore, are of concern. All seed planter (secondary handler) combined short- and intermediate-term dermal and inhalation exposure scenarios assessed resulted in an ARI > 1 at some level of personal protection and, therefore, do not present risk estimates of concern.

EPA has assessed short- and intermediate term occupational post-application dermal exposure and risk for any crops which reentry into an area previously treated with chlorpyrifos is anticipated. The assessment was completed using 7 chemical-specific registrant submitted dislodgeable foliar residue (DFR) studies.

The MOEs estimated for liquid spray and granular formulation reentry are not of concern (i.e., an MOE $\geq$ 100) in the range of 0 to 4 days for lower to medium exposure activities and 0 to 8 days for high exposure activities, with the greater majority falling between 0 to 4 days when all exposure activities are considered. HED also estimated the MOEs for reentry into microencapsulated and total release fogger formulation treated greenhouses. These estimates range from 0 to > 35 days after treatment (the completion of the monitoring period) for all exposure activities considered.

A quantitative occupational post-application inhalation exposure assessment was not performed for chlorpyrifos. An inhalation exposure assessment was performed for occupational/commercial handlers and handlers are expected to have greater exposures than workers involved in post-application activities. The handler assessment is currently considered a worst-case assessment for post-application exposure.

Occupational/Residential Exposure to Chlorpyrifos Oxon

The Agency has considered the potential for occupational and residential exposure to chlorpyrifos oxon. Workers re-entering an environment previously treated with chlorpyrifos (occupational post-application) and the general population residing near chlorpyrifos application sites (bystanders) could potentially be exposed to the oxon as chlorpyrifos is degraded in the

environment. Dermal exposure to the oxon could occur through contact with chlorpyrifos treated surfaces and inhalation exposure through airborne oxon. However, the likelihood of exposure to the oxon is slight due to its rapid deactivation to TCP (3,5,6-trichloro-2-pyridinol). In an effort to further explore the potential for oxon exposure, EPA has researched and reviewed all available information sources. Based upon this review, EPA intends to require additional studies to address uncertainties regarding the formation of chlorpyrifos oxon in the air post-application and its formation and decay in greenhouses.

Comparison of the Chlorpyrifos Occupational Assessment (June 2000 Assessment and the 2011 Preliminary Assessment)

For comparison purpose, a range of resulting occupational handler risk estimates (MOEs) are presented for both the current preliminary (2011) chlorpyrifos assessment and the June 2000 chlorpyrifos assessment. The range represents a low, medium, and high exposure scenario. Also presented is a range of personal protection (single layer/gloves, double layer/gloves, and engineering controls). [See Table 28(dermal) and Table 29 (inhalation).]

The dermal handler risk estimates remain virtually unchanged between the 2000 and 2011 assessments since the dermal PoD is the same (NOAEL of 5 mg/kg/day from a dermal study). The 2008 SAP concurred with the selection of this PoD for assessing dermal scenarios.

The inhalation PoD in 2000 was 0.1 mg/kg/day (LOAEL/NOAEL based on 90 day inhalation studies and DNT). That same PoD is used in the current assessment except that it has been converted to an HEC (human equivalent concentration). This resulted in the reduction of the default database uncertainty factor for interspecies extrapolation from a 10x to a 3x. Thus the level of concern MOE for this assessment is 30 (compared to 100 in 2000). In addition the NOAEL was corrected to account for an 8 hour workday because worker exposure is expected to occur during the course of an average workweek (8 hours/day and 5 days/week; animals were exposed 6 hours a day in the study). The inhalation handler risk estimates have changed since the 2000 assessment. This can be mainly attributed to the use of the HEC in the preliminary assessment.

Note that the actual dermal and inhalation MOEs presented in the 2000 assessment may differ somewhat than those presented here since some of the exposure assumptions used today may vary due to refinements made since 2000. The 2011 exposure assumptions were compared to the 2000 PoD for illustrative purposes only.

2.0 HED Recommendations

2.1 Data Deficiencies

Toxicology

870.6300: Developmental Neurotoxicity (MRID 44556901). While the offspring NOAEL and LOAEL have not yet been identified for this developmental neurotoxicity study, it is recognized

that the study was well-conducted according to Agency guideline §83-6, and under GLP regulations. Remaining questions can be resolved with additional information and statistical analysis, but there are no outstanding concerns regarding the quality of the animal data. The study is currently classified as "guideline-unacceptable, but upgradeable". The study may be upgraded to "acceptable" pending submission and review of additional morphometric data for PND 66 low-dose females (parietal cortex and hippocampus measurements) (S. Makris, 3/3/00, TXR. 0014014, D254907).

Residue Chemistry

860.1500: Magnitude of the residue studies with lemon after application of Lorsban 4E and 75% WDG formulations separately to reassess the tolerance for the citrus fruit crop group; Magnitude of the residue studies to establish a tolerance for wheat hay.

860.1520: Processing studies for: cotton meal, hulls and refined oil and for soybean meal, hulls and refined oil.

Labels: Revise the corn and cotton use restrictions in the chlorpyrifos labels to eliminate feeding restrictions in treated areas. Maintain only dormant/delay dormant and trunk spray applications for tart cherries in the label of the 75% WDG end use product.

Tolerances:

The following tolerances for chlorpyrifos are necessary to address residues found in field trails:

Cotton, gin byproducts…… 15 ppm
Grain, aspirated fractions……..22 ppm
Corn milled byproducts……... 0.1 ppm
Wheat milled byproducts…… 1.5 ppm

Revocation of the chlorpyrifos tolerance for lettuce (no registered uses; revocation pending).

Modification of the tolerance expression for chlorpyrifos in the 40 CFR 180.342 is needed to comply with the Interim Guidance for Writing Tolerance Expressions.

Occupational/Residential Exposure

The Agency intends to require additional data to address uncertainties regarding the formation of chlorpyrifos oxon in the air post-application and its formation and decay in greenhouses. In addition, several data gaps were identified in the Registration Eligibility Decision (RED) for the occupational and residential assessment of chlorpyrifos (finalized 7/31/06; IRED issued 2/2002). The only one of these requirements that has not been satisfied is the requirement for a study confirming the area treated for sod farm chlorpyrifos treatment. This requirement remains outstanding.

2.2 Tolerance Considerations

2.2.1 Enforcement Analytical Method

The methods in the PAM Volume II are adequate to analyze the residue of concern for tolerance enforcement purposes, chlorpyrifos only. The limit of detection of these methods is adequate to cover the lowest tolerance level included in the 40 CFR 180.342 for detection of chlorpyrifos only, 0.01 ppm. In addition, chlorpyrifos is completely recovered using FDA multiresidue protocols D and E (nonfatty matrices) and partially recovered using multiresidue method protocol E (fatty matrices).

2.2.2 International Harmonization

Current US permanent tolerances for chlorpyrifos are listed in 40 CFR§180.342 and are summarized in the residue chemistry chapter and in Appendix C of this document. The Codex Alimentarius Commission and Canada have established Maximum Residue Limits (MRLs) for chlorpyrifos. Mexico adopts US tolerances and/or Codex MRLs for its export purposes. US tolerances and Codex MRLs are based on the analysis of residues of chlorpyrifos. Canada MRLs are for chlorpyrifos for some commodities and for both parent chlorpyrifos and its metabolite TCP (3,5,6-trichloro-2-pyridinol; not a US residue of concern) for other commodities.

With the exception of apple commodities, harmonization with the Canada MRLs is not possible as the Canadian residue definition is for the combined residues of chlorpyrifos and TCP (in the US TCP is not considered a residue of concern for chlorpyrifos risk assessment or tolerance enforcement). Harmonization between the USA tolerances and Codex MRLs is only possible for corn, field, grain; cranberry; egg; sorghum, grain, grain; sorghum, grain, stover; and wheat, grain. In addition, two commodities of the Leafy Vegetable (CG 5) can be harmonized with the Codex, head cabbage, and Chinese cabbage (type petsai). A summary of the US and international tolerances and MRLs is included in Appendix C of this document.

2.2.3 Recommended/Reassessed Tolerances

The following tolerances would need to be established to address residues found on the following commodities in new crop field trial data received as part of the chlorpyrifos 2003 DCI:

Table 1 Recommended Tolerances for Chlorpyrifos

Commodity	Established Tolerance (ppm)	Recommended Tolerance (ppm)	Comments *Correct Commodity Definition*
Aspirated grain fractions	NA	22	
Cotton, gin by-products	NA	15	

On 5/27/09 HED established interim guidance on writing tolerance expressions for enforcement purposes. In order to add clarity to the language used to establish the coverage of the tolerance expression and measurement of the level of the residue in the RACs the text in the 40 CFR § 180.342 should read: "(a) General. (1) Tolerances are established for residues of chlorpyrifos, including its metabolites and degradates, in or on the commodities in the table below.

Compliance with the tolerance levels specified below is to be determined by measuring only chlorpyrifos." The current tolerance expression reads "chlorpyrifos *per se* (*O,O* -diethyl *O* -(3,5,6-trichloro-2-pyridyl) phosphorothioate".

2.3 Recommendations from Residue Reviews

The following recommendations were made in I. Negrón-Encarnación, 5/24/11, D388164, *Chlorpyrifos. Registration Review Action for Chlorpyrifos. Summary of Analytical Chemistry and Residue Data.*

Revise the corn and cotton use restrictions in the chlorpyrifos labels to eliminate feeding restrictions in treated areas.

The following tolerances for cotton gin byproducts and aspirated grain fractions are necessary to address residues found in field trails:

Cotton, gin byproducts ..... 15 ppm
Grain, aspirated fractions .....22 ppm

Maintain only dormant/delay dormant and trunk spray applications for tart cherries in the label of the 75% WDG end use product.

Revocation of the tolerance for lettuce is in process as uses of chlorpyrifos in this crop are not included in the label for the registered products.

Magnitude of the residue studies are needed with lemon after application of Lorsban 4E and 75% WDG formulations separately to reassess the tolerance for the citrus fruit crop group.

Magnitude of the residue studies are needed to establish a tolerance for wheat hay.

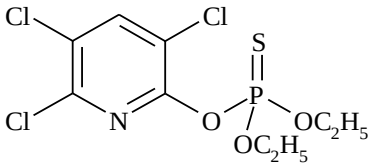
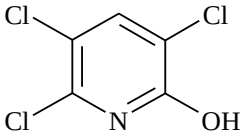
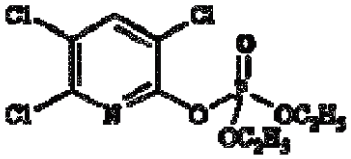
Processing studies are needed for:
Cotton meal, hulls and refined oil
Soybean meal, hulls and refined oil

Tolerances are needed to address residues of chlorpyrifos on:
Corn milled byproducts as 0.1 ppm
Wheat milled byproducts as 1.5 ppm

Modification of the tolerance expression for chlorpyrifos in the 40 CFR 180.342 is needed to comply with the Interim Guidance for Writing Tolerance Expressions.

3.0 Introduction

3.1 Chemical Identity

Table 2 Chlorpyrifos Degradate/ Residues of Concern Nomenclature.	
Chlorpyrifos	
IUPAC name	*O,O*-diethyl *O*-3,5,6-trichloro-2-pyridyl phosphorothioate
CAS name	*O,O*-diethyl *O*-(3,5,6-trichloro-2-pyridinyl) phosphorothioate
CAS registry number	2921-88-2
End-use product (EP)	Lorsban 75% WDG and Lorsban 50% WP
TCP Metabolite/Degradate (Residue of Concern for Canada) IUPAC Name 3,5,6 Trichloro-2-pyridinol	
Oxon Metabolite/Degradate Common Name Chlorpyrifos Oxon IUPAC Name O,O-diethyl. O-3,5,6-trichloro-2-pyridyl	

3.2 Physical/Chemical Characteristics

Technical chlorpyrifos is a white crystalline solid. Chlorpyrifos is stable in neutral and acidic aqueous solutions; however, stability decreases with increasing pH. Chlorpyrifos is practically insoluble in water, but is soluble in most organic solvents (i.e., acetone, xylene and methylene chloride). Chlorpyrifos is moderately volatile based on its vapor pressure of 1.87×10^{-5} mmHg at 25^{o}C.

In the environment, hydrolysis is not expected to play a significant role in chlorpyrifos dissipation; however, under alkaline conditions laboratory studies show chlorpyrifos is susceptible to hydrolysis. Laboratory studies suggest that volatilization and photodegradation are not likely to play a significant role in the dissipation of chlorpyrifos in the environment. Nonetheless, chlorpyrifos has been detected in air samples so volatilization may play more of a role in dissipation than laboratory studies indicate. The major route of dissipation appears to be aerobic and anaerobic metabolism. Based on available data, chlorpyrifos degrades slowly in soil under both aerobic and anaerobic conditions. Degradation begins with cleavage of the phosphorus ester bond to yield 3,5,6-trichloro-2-pyridinol (TCP). Field dissipation studies show that chlorpyrifos is moderately persistent under field conditions—dissipation half-life less than 60 days. Chlorpyrifos is only slightly soluble in water but once it reaches aquatic environments

the Log K_{ow} (4.7) indicates that chlorpyrifos may bioaccumulate in fish and other aquatic organisms. A fish bioaccumulation study shows that chlorpyrifos is absorbed by fish; however, it rapidly depurates when exposure ceases.

Oxidation of chlorpyrifos to chlorpyrifos oxon could potentially occur through photolysis, aerobic metabolism, and chlorination as well as other oxidative processes. Chlorpyrifos oxon is expected to have similar fate characteristics as chlorpyrifos except chlorpyrifos oxon is more soluble in water and undergoes hydrolysis faster. The hydrolysis half-life of chlorpyrifos oxon is significantly shorter than that observed for chlorpyrifos. Chlorpyrifos oxon hydrolyses to form TCP. For chlorpyrifos, water purification (chlorination) has been shown to be a major route of chlorpyrifos oxon formation.

3.3 Anticipated Exposure Pathways

Humans may be exposed to chlorpyrifos in food and water since applications may be made directly to growing crops (food and feedstuffs) which could also result in chlorpyrifos reaching surface and ground water sources of drinking water. Registered uses that may result in residential (non occupational) exposures include aerial and ground-based fogger adult mosquitocide applications and golf course turf applications. There is also a potential for residential bystander exposure from field volatilization of applied chlorpyrifos. In occupational settings, exposure may occur while handling the pesticide prior to application, as well as during application. There is also a potential for post-application exposure for workers re-entering treated fields.

3.4 Consideration of Environmental Justice

Potential areas of environmental justice concerns, to the extent possible, were considered in this human health risk assessment, in accordance with U.S. Executive Order 12898, "Federal Actions to Address Environmental Justice in Minority Populations and Low-Income Populations," (http://www.eh.doe.gov/oepa/guidance/justice/eo12898.pdf. As a part of every pesticide risk assessment, OPP considers a large variety of consumer subgroups according to well-established procedures. In line with OPP policy, HED estimates risks to population subgroups from pesticide exposures that are based on patterns of that subgroup's food and water consumption, and activities in and around the home that involve pesticide use in a residential setting. Extensive data on food consumption patterns are compiled by the USDA under the Continuing Survey of Food Intake by Individuals (CSFII) and are used in pesticide risk assessments for all registered food uses of a pesticide. These data are analyzed and categorized by subgroups based on age, season of the year, ethnic group, and region of the country. Additionally, OPP is able to assess dietary exposure to smaller, specialized subgroups and exposure assessments are performed when conditions or circumstances warrant. Whenever appropriate, non-dietary exposures based on home use of pesticide products and associated risks for adult applicators and for toddlers, youths, and adults entering or playing on treated areas post-application are evaluated. In addition to the aforementioned exposure settings and population subgroups, the current chlorpyrifos risk assessment considered exposures to bystanders as a result of field volatilization of applied chlorpyrifos.

4.0 Hazard Characterization and Dose-Response Assessment

4.1 Toxicology Studies Available for Analysis

The toxicological database for chlorpyrifos is extensive and is adequate to support the registration review. Since the 2002 IRED/2006 RED, and in addition to many studies in the scientific literature, three new studies have been submitted to OPP: a special acute inhalation study (MRID 48139303), a comparative cholinesterase assay (MRID 48139301), and an immunotoxicity study (MRID 48139304). These submitted studies have been reviewed and found to be acceptable to support the chlorpyrifos risk assessment. The toxicity profiles and executive summaries of all submitted studies are listed in Appendix A.

The database spans multiple routes of exposure, animal species, and lifestages and consists of acute toxicity, subchronic oral, subchronic inhalation, immunotoxicity, developmental toxicity, multi generation reproduction, chronic feeding/carcinogenicity, dermal toxicity, metabolism, pharmacokinetic, acute and subchronic neurotoxicity, and developmental neurotoxicity studies. The genetic toxicity/mutagenicity database has been evaluated. In addition, special studies have been submitted including an acute neurotoxic esterase rat study, cognitive rat study, comparative cholinesterase assay where PND11 pups and adults were assessed (for both parent chlorpyrifos and its oxon metabolite) and an acute inhalation study.

In addition to the above submitted chlorpyrifos studies there are numerous literature studies available on various aspects of chlorpyrifos including inhibition of cholinesterase, neurological effects in animals and humans following gestational and post-natal exposures, pharmacokinetics, mechanism of action, as well as studies with adult human volunteers for ChE inhibition. Many of these studies were discussed at the 2008 SAP meeting and details are provided on the Science Advisory Panel website (http://www.epa.gov/scipoly/sap/meetings/2008/091608_mtg.htm). EPA plans to finalize the science documents reviewed by the SAP in the upcoming months. However, the advice received by the Agency at the 2008 SAP meeting has been used to inform the selection of toxicological points of departure for use in this preliminary chlorpyrifos risk assessment.

4.2 Absorption, Distribution, Metabolism, & Elimination (ADME)

The metabolism and toxicokinetics (TK) of chlorpyrifos have been extensively studied in animals and humans as well as in vitro systems. Overall, rats and humans show similar patterns of metabolism for chlorpyrifos in adults.

Chlorpyrifos undergoes metabolic transformations mainly by the liver microsomal enzymes. Although, chlorpyrifos is lipophilic, its extensive metabolism into water soluble metabolites does not lead to accumulation of the parent material or its metabolites in the body tissues. The initial metabolic attack on the chlorpyrifos is its desulfuration, resulting in its bioactivation to the more toxic and potent ChE inhibitor, the oxon form. However, the oxon is unstable and is rapidly deactivated through hydrolytic cleavage by a process called dearylation releasing the 3,5,6-trichloro-2-pyridinol (TCP). Simultaneously along the desulfuration process, dearylation will be acting on both the parent chlorpyrifos as well as on the oxon metabolite leading to the release of

TCP. TCP is further conjugated to form glycine or glucuronide conjugates and eliminated into the urine. TCP is the major excreted metabolite and used as the major biomarker in pharmacokinetic, biomonitoring, and epidemiology studies.

There are several enzymes that play a role in the metabolism and toxicity of chlorpyrifos. In addition to inhibition of ChE, the oxon also binds stoichometrically to butyrlcholinesterse (BuChE; abundant in blood and other tissues). In this regard BuChE is viewed as a scavenger of the oxon formed and may prevent it from entering the brain or peripheral targets for inhibition of ChE. The cytochrome P450 family of microsomal enzymes (CYPs) is responsible for its metabolic activation and deactivation. The oxon also binds irreversibly to carboxylesterases. Carboxylesterases are distributed among different issues (liver, blood, brain) with highest abundance in the liver. The glutathione dependent enzymes play an important role in the secondary metabolism of chlorpyrifos producing water soluble metabolites that are readily excreted into the urine. Finally, another group of important enzymes in the detoxification of chlorpyrifos is the A-esterases; one such A-esterase is paraoxonase (i.e., PON1). These are calcium activated enzymes and are distributed in various tissues including the liver, brain and blood. These act on the oxon by hydrolyzing it before reaching its target AChE enzyme. Some have suggested that PON1 status is a determining factor in susceptibility to chlorpyrifos (Cole et al, 2005; Berkowitz et al, 2004; Wolff et al, 2007; Furlong et al, 2005; Brophy et al, 2001; Holland et al, et 2006; Chen et al, 2003).

The increased sensitivity of the young from acute exposure is likely attributed to a reduced capacity to detoxify chlorpyrifos in juvenile animals (Gagne and Brodeur, 1972; Benke and Murphy, 1975; Pope *et al*., 1991; Chambers and Carr, 1993; Padilla *et al*., 2000; 2002; Karanth and Pope, 2000). Specifically, in rats, A-esterase activity is virtually nonexistent in the fetus (Lassiter *et al*., 1998) and increases from birth reaching adult levels around PND21 (Mortensen *et al*., 1996; Li *et al*., 1997). Mortensen et al (1996) showed that the plasma level of CPOase[1] in PND21 pups was 1/11 that of adult animals. The animal data regarding the role of carboxylesterase in mediating OP toxicity are also quite extensive (e.g., Clement, 1984; Fonnum et al., 1985; Maxwell, 1992 a, b). Fetal rats possess very little carboxylesterase activity (Lassiter et al., 1998) with increasing activity seen as the postnatal rat matures, reaching adult values after puberty (50 days-of-age; Morgan et al., 1994; Moser et al., 1998; Karanth and Pope, 2000). There are, however, very little data in human tissues which could evaluate age-related maturation of carboxylesterase expression. The available data come from Pope et al (2005) and Ecobichan and Stephens (1973). Ecobichan and Stephens (1973) showed a steady increase in AChE and ChE levels of infants beginning at birth up to adult levels. Pope et al (2005) evaluated maturational expression of liver carboxylesterases in human liver tissues from infants (2–24 months) and adults (20–36 years). The authors report relatively small (and not statistically significant) differences in activities between children ages 2–24 months and adults (20–36 years). The Agency notes, however, that youngest age evaluated in the study was 2 months old and this individual had the lowest level of carboxylesterase.

There is a clear age-dependant sensitivity which diminishes as the pups mature; this pattern is likely reflective of the metabolic processes which rapidly mature in the rat pup. The SAP

[1] CPOase is A-esterase (PON1) activity specific to chlorpyrifos oxon

concurred with the Agency that juveniles are more sensitive than adults to ChE inhibition following acute exposures, but not necessarily for repeated exposures.

In 2008, the Agency solicited comments from the SAP on the use of information on PON1 to inform the intra-species extrapolation factor. The SAP panel agreed with EPA that PON1 status cannot be ruled out as a determinant of chlorpyrifos toxicity, and there appears to be a different susceptibility between fetuses and neonates compared to adults. The Panel did not support using such PON1 information alone to address population sensitivity, but instead suggested that PBPK modeling which accounts for all the metabolizing enzymes is a more supportive approach.

In the rat, chlorpyrifos is excreted primarily in the urine (84%) with lesser amounts excreted in the feces (5%) within 72 hours. The metabolism of chlorpyrifos is extensive, and no unchanged parent compound is found in the urine. The major urinary metabolites were 3,5,6-TCP (TCP) and glucuronide and sulfate conjugates of TCP. In humans (adult males) approximately 70% of chlorpyrifos is excreted in the urine as conjugated TCP within 5 days following acute oral exposure, and the dermal absorption is 1 to 3% in this study (Nolan *et al*. 1982, Accession No. 249203). The mean pharmacokinetic half-life for TCP in the urine is approximately 27 hours following both oral and dermal exposure.

There are some limited data that show that chlorpyrifos can be found in breast milk. Chlorpyrifos is lipophillic and has a Log Kow of 4.7, which would indicate a potential to accumulate in milk. Mattsson *et al*. (1998, 2000) provided data in rat milk which suggest that chlorpyrifos can reach milk at doses of 0.3 mg/kg/day. There is public literature that indicates that chlorpyrifos may be found in human breast milk in the U.S. (Casey 2005) and India (Srivastava *et al*., 2011). The degree to which the Indian data are relevant in the U.S. is unknown (and unlikely reflective of the general population exposed to chlorpyrifos in food/water).

Toxicokinetic (TK) studies from humans and rats show that chlorpyrifos and/or its metabolites may be available to the fetus, likely at levels similar to maternal tissues (Whyatt *et al*, 2003; Hunter al, 1999; Mattsson *et al*, 1998, 2000; Akhtar *et al*, 2006). In the 2008 draft issue paper, the Agency summarizes the studies which show that TK differences in young and adults play a key role in the age-dependant sensitivity with chlorpyrifos. Moreover, the 2008 document provides additional information in pregnant animals and humans which suggest that metabolic capacity to detoxify chlorpyrifos may be reduced during pregnancy, although the relevance of these changes is not known at low environmental levels. The Panel supported the Agency's conclusions on the role of lifestage ontogeny in potential sensitivity to chlorpyrifos and the potential that pregnant females may be more sensitive to chlorpyrifos than males (FIFRA SAP, 2008), Recent results of EPA's analyses (see BMD Appendix E) for rat data suggest that pregnant females are approximately 2-12 fold more sensitive than non-pregnant adult females, as shown in Table 3 below.

Table 3 Comparison of Cholinesterase Inhibition for Adult Pregnant Female and Non-Pregnant Rats

Endpoint	Response	Comments
Repeated Dose ChEI - male and female rats (Hoberman et al. 1998 a, b, MRID 44556901; Mattsson et al. 1998, MRID 44648101; Maurissen et al. 2000; Marty and Andrus (2010; DAS CCA MRID 48139301; 4807001)	Female rats, 11 days (CCA): $BMD_{10}/BMDL_{10}$: RBC ChEI: 0.45/0.35 brain ChEI: 1.03/0.95 mg/kg/day Female pregnant rats GD6-20; 15 days (DNT): $BMD_{10}/BMDL_{10}$: RBC ChEI: 0.06/0.03 mg/kg/day brain ChEI: 0.65/0.54 mg/kg/day	Pregnant female rats more sensitive than non-pregnant female rats for RBC and brain ChEI: RBC ChEI: 7.5-12 fold more sensitive Brain ChEI: 1.6-1.8 fold more sensitive

DNT= developmental neurotoxicity study
CCA= comparative cholinesterase study

4.3 Toxicological Effects

Cholinesterase (ChE) Inhibition. Chlorpyrifos, like other OPs, binds to and phosphorylates the enzyme, acetlycholinesterase (AChE), in both the central (brain) and peripheral nervous systems leading to accumulation of acetylcholine in critical neuronal junctions and, ultimately, to clinical signs of toxicity. This mode of action, in which ChE inhibition leads to neurotoxicity, has been well described (Mileson *et al*., 1998, Eaton *et al*., 2008; Gupta, 2011). In 2000, the Agency concluded for chlorpyrifos that inhibition of ChE provides the most sensitive dose response data in all of the animal species evaluated (rats, mice, rabbits dogs) and in humans, regardless of exposure duration and route of exposure. The available data indicate that humans are more sensitive than animals to ChE following both oral and dermal exposure (Nolan *et al*. 1982, USEPA 2000a). Numerous ChE studies are available in different lifestages and ages in rats, which were included in the 2000 risk assessment and/or discussed at the 2008 FIFRA SAP (http://www.epa.gov/scipoly/sap/meetings/2008/091608_mtg.htm). These studies vary widely by the level and number of doses used, availability of time course information, and method of administration. The Agency has reviewed the studies submitted for registration as well as searched the public literature for studies in which adult animals and/or juvenile animals were exposed to chlorpyrifos. ChE inhibition is most commonly reported for the blood (plasma and RBC) and brain (whole or subsections). The chlorpyrifos database is unique since it includes evaluations of peripheral tissues such as the heart, diaphragm, or lung. In animals, significant inhibition of plasma and red blood cell (RBC) ChE occur at doses below those that cause brain ChE inhibition. Following inhalation exposure, inhibition of ChE in the lung was more sensitive than either RBC ChE or brain ChE inhibition.

With respect to considering the response of sensitive lifestages to ChE inhibition, the Agency has reviewed numerous repeated gestational exposure ChE studies for chlorpyrifos and other OPs. Overall, these gestational studies show that the fetus exhibits no more ChE inhibition than does the dam and in some studies fetus actually exhibits less inhibition (USEPA, 2008; USEPA,

2006). However, ChE data in fetuses from repeated dosing gestational studies may not accurately reflect potential fetal toxicity at a particular dose (USEPA 2008, draft chlorpyrifos hazard and dose-response characterization). The FIFRA SAP concurred with the Agency's conclusion with respect to interpreting ChE data from *in utero* exposures. As part of the scientific analysis presented at the 2008 SAP meeting, the Agency showed acute brain post-natal ChE studies ranging from PND1 to PND33. There is a clear age-dependant sensitivity which diminishes as the pups mature; this pattern is likely reflective of the metabolic processes which rapidly mature as the rat pup matures. The SAP concurred with the Agency that juveniles are more sensitive than adults to ChE inhibition following acute exposures, but not necessarily for repeated exposures.

The SAP also supported that pregnant animals and humans may be somewhat more sensitive to ChE inhibition from chlorpyrifos than non-pregnant adults based on a reduced capacity of key detoxification enzymes (e.g., paraoxonase, P450 isozymes) in modulating levels of chlorpyrifos in animal studies. It is unknown if the relatively small differences in enzyme levels is important at environmental exposure levels. As noted previously, pregnant rats were about 2-12 fold more sensitive than non pregnant rat females for ChE inhibition (See Table 3).

The Agency has recently reviewed an acute and repeat special non-guideline comparative cholinesterase (CCA) study, and an acute inhalation study. The CCA study was conducted to compare the relative toxicity of chlorpyrifos and chlorpyrifos oxon in both juvenile (PND11 pups) and adult rats based on ChE inhibition (Marty and Andrus 2010, MRID No.: 48139301 TXR No. 0055409). Both acute (single) dosing and a repeat 11-day exposure scenario were evaluated for chlorpyrifos and chlorpyrifos oxon. In the acute subpart, juvenile rats were dosed with chlorpyrifos via both gavage and milk. This study is considered high quality, and provides reliable measures of blood and brain ChE at the time of peak effect (6-8 hours post-dosing), use 4-6 doses and use a wide range of doses. The Agency notes that the timing of ChE measurement in this study (8 hrs for milk) is later than other studies that report the peak at between 3-6 hours but is supported by time course data collected as part of this study for 3-10 mg/kg dose levels [see EPA 2008, draft appendix C, Mode of action, inhibition of acetylcholinesterase (AChE)]. The Agency used these data to conduct benchmark dose (BMD) analysis. Following acute exposure, based on BMD analysis, PND11 pups were more sensitive than adults at 10% RBC ChE inhibition (BMD10 are 0.5 mg/kg/day and 1.9 mg/kg/day, respectively), and 10% brain ChE inhibition (BMD10 are 1.4 and 4.1 mg/kg/day, respectively) for chlorpyrifos. For acute chlorpyrifos-oxon exposure, pups were also more sensitive for RBC ChE inhibition than adults (BMD10s are 0.08 and 0.21 mg/kg/day for pups and adults, respectively). Pups were more sensitive to ChE inhibition following milk exposure than from gavage dosing based on BMD10s. Following 11 days of repeated dosing, PND11 pups were slightly more sensitive than adults to chlorpyrifos based on BMD10s for RBC ChE inhibition (0.45 mg/kg/day for adults vs 0.11-0.17 mg/kg/day for pups), but not for chlorpyrifos oxon. There was no inhibition of the brain ChE reported for the oxon at any dose up to 1 mg/kg for acute dosing and 0.5 mg/kg/day following repeat dosing in either pups or adults. The timing of measurement for the oxon was 4 hours post-dosing in this CCA. Other literature studies have reported the time of peak brain ChE inhibition was 1 hour post dosing (Betancourt and Carr 2004).

In a special acute inhalation study female rats were exposed by nose only to atmospheric concentrations of up to 53.9 mg/m^3 of particulate chlorpyrifos for six hours and allowed an additional 72 hours to recover (MRID No: 48139303 Hotchkiss *et al*. 2010, TXR # 0055409.). The peak inhibition for plasma and RBC ChE was at 2 hours post-dosing. Consistent and significant lung and plasma ChE inhibition were noted at the lowest concentration tested of 3.7 mg/m^3, which is a LOAEL. RBC and brain ChE inhibition were noted at ≥ 12.9 mg/m^3 and 53.9 mg/m^3, respectively, indicating they are less sensitive than lung and plasma ChE inhibition following acute inhalation exposures. It should be noted, however, that the lung may contain both butyrl and acetyl cholinesterase, which may partially explain the sensitivity of the lung ChE inhibition. No NOAEL was established. A BMD analysis was attempted but did not provide high confidence results due to the nature of the dose response data. The RBC ChE data had significant temporal variation and thus a reliable fit was not achieved. For the lung ChE data, no statistically reliable fit was obtained with exponential modeling using nonhomogeneous variance (suggested by BMD statistical results). However, a reliable fit was obtained with a homogeneous variance model. This analysis supports retention of a 10X LOAEL to NOAEL uncertainty factor for the single- day bystander inhalation risk assessment. Using the Agency's Reference concentration (RfC) methodology, a human equivalent concentration (HEC) was calculated to be 0.62 mg/m^3 based on the LOAEL of 3.7 mg/m^3.

Developmental Effects. There is a large body of literature on the effects of chlorpyrifos in the developing brain of laboratory animals (rats and mice) indicating that gestational and/or early postnatal exposure to chlorpyrifos may cause persistent behavioral effects into adulthood. These data provide support for the susceptibility of the developing rodent brain to chlorpyrifos exposure. Many of these studies were reviewed by EPA in the 2000 risk assessment and for the 2008 SAP (USEPA 2000b, 2008). The SAP concurred with the Agency's conclusion that in rats, chlorpyrifos causes alterations in brain development in offspring of exposed mothers. Studies in the peer reviewed literature and results of the guideline developmental neurotoxicity (DNT) study are supportive of the possibility that chlorpyrifos exposure may affect brain development (e.g., altered synaptic development, alterations in DNA, RNA, and protein synthesis, inhibition of mitosis and mitotic figures, disruption of the structural architecture of the brain). Studies from multiple laboratories in two rodent species provide evidence that adults may exhibit persistent behavioral changes following perinatal exposures. Since several laboratories included a dose of 1 mg/kg/day, some comparisons in response may be made – these are summarized in Table 4 below. Chlorpyrifos studies in rats and/or mice have reported impaired cognition (spatial learning and working memory); changes in locomotor activity levels (exploration, rearing); and altered social interaction (aggression, maternal behavior). It is notable that the laboratory animal studies vary in experimental designs such as species, strain, gender, dosing regimens (age, routes, vehicle), and test parameters. However, in animals, the doses (1 and 5 mg/kg/day) most often used in the behavior studies are sufficient to elicit approximately ≥10% brain inhibition and ≥30% in RBC inhibition, depending on the study design and the age of the animal. The results of these studies contribute to the overall hazard characterization of chlorpyrifos but are not useful in deriving PoD for risk assessment; the SAP concurred with the Agency's proposed use of the behavioral studies.

Table 4 Summary of Tests and Outcomes in Adults (at least 5 weeks of age, males and/or females) Following Gestational and/or Postnatal Dosing of 1 mg/kg/day Chlorpyrifos.

Behavioral Domain	Device/Task	Outcomes	Species	Reference
Locomotor activity	Figure-8 maze	Decreased habituation rate	Rat	Levin et al., 2002
	Open-field	Increased activity	Mouse	Ricceri et al., 2003
	Elevated plus maze	Increased crossings Decreased crossings	Rat Mouse	Aldridgeet al., 2005c Braquenier et al., 2010
	T maze	Decreased activity	Rat	Icenogle et al., 2004 Levin et al., 2001, 2002
Learning & Memory	Radial arm maze	Increased errors	Rat	Levin et al., 2002 Aldridge et al., 2005c Johnson et al., 2009
	Morris water maze	Slower learning	Mouse	Billauer-Haimovitch et al., 2009
	Foraging in radial arm maze	Slower learning	Mouse	Haviland et al., 2010
Social Interactions (mice)	Agonistic behaviors (male)	Increased	Mouse	Ricceri et al., 2003, 2006
	Induced maternal behaviors (female)	Altered	Mouse	Ricceri et al., 2006
Anxiety/ Depression	Elevated plus maze	Increased time in open arms Decreased time in dark arms	Rat Mouse	Aldridge et al., 2005c Braquenier et al., 2010
	Light/dark box	Decreased time in light side	Mouse	Braquenier et al., 2010

Over the last 15 years, biologically plausible hypotheses for chlorpyrifos have been proposed by researchers. These include effects on signaling pathways (Slotkin, 2006), a morphogenic role of AChE effect the structure of the brain (Brimijoin and Koenigsberger, 1999 and Bigbee et al, 1999; Yang *et al*, 2008) and recently a reduction in axonal transport mediated through impaired tubulin polymerization (Prendergast *et al*, 2007; Grigoryan *et al*, 2008; Grigoryan *et al* 2009; Grigoryan and Lockridge, 2009; Jiang *et al*, 2010) Although multiple mechanisms have been proposed, a coherent mode of action with supportable key events, particularly with regard to dose-response and temporal concordance, has not yet been elucidated. The Agency continues to evaluate new studies on chlorpyrifos and if sufficient information becomes available to perform such an MOA analysis, the Agency may do so in the future. In 2008, the SAP supported the Agency's conclusions that there were insufficient data to clearly identify a specific MOA for effects in the developing nervous system. Some panel members indicated that the data cited in

Eaton *et al*. (2008) could be useful in evaluating alternative (e.g., non-cholinergic) modes of action.

Chlorpyrifos was evaluated for prenatal developmental toxicity in rats, mice and rabbits. In one rat study, developmental effects (increased postimplantation loss) were noted at 15 mg/kg/day (highest dose tested, HDT), that were also associated with maternal toxicity, while another rat study failed to observe similar developmental effects at 15 mg/kg/day. Developmental effects were also noted at higher doses in mice at 25 mg/kg/day (minor skeletal variations, delayed ossification and reduced fetal weight and length) and rabbits at 140 mg/kg/day (decreased fetal weights and crown rump lengths, and unossified xiphisternum and/or 5th sternebra). However, in both mice and rabbits, the developmental effects occurred at maternally toxic doses as indicated by reduced weight gain, and food consumption in both species, and increased mortality in mouse dams.

In the rat developmental neurotoxicity study, chlorpyrifos was associated with alterations in brain development in offspring of exposed mothers. Specifically, pups of the 1 mg/kg/day group exhibited significant decreases in measurements of the parietal cortex in female offspring at postnatal day 66. The only maternal effect at this dose was plasma and RBC ChE inhibition during the treatment period. At higher doses, pups of the 5 mg/kg/day group exhibited decreased body weight/body weight gain and food consumption in both sexes, reductions in pup viability, delays in development, decreased brain weight and morphometric alterations in the brain. However, these effects were observed in the presence of maternal toxicity as evidenced by fasciculations, hyperpnea and hyperactivity, in addition to reduced body weight gain.

Reproductive Effects. Chlorpyrifos induced reproductive toxicity in one generation of rats, but only at dose levels that induced parental toxicity. Reproductive effects in the F1 generation included reduced pup weights and increased pup mortality that corresponded to slightly but significantly reduced body weight gain in their parental F0 dams during lactation days 1-21. In addition, parental toxicity was characterized by inhibition of plasma, RBC and brain cholinesterase activities as well as histological lesions of the adrenal gland (vacuolation of cells of the zona fasciculata).

Carcinogenicity/Genotoxicity. Chlorpyrifos is not likely to be carcinogenic to humans, based on the lack of evidence of carcinogenicity in studies in rats and mice and the absence of a mutagenicity concern. Chlorpyrifos was not mutagenic in bacteria, or mammalian cells, but did cause slight genetic alterations in yeast and DNA damage to bacteria.

Immunotoxicity. There was no sign of immunotoxicity in the guideline study at the highest dose tested.

4.4 Epidemiology

4.4.1 Three Major Epidemiological Prospective Studies in Mothers and Their Children

There are three major prospective epidemiology cohort studies evaluating pre- and post-natal pesticide (chlorpyrifos and/or OPs) exposure in mother-infant pairs with birth outcomes, and

childhood neurobehavioral and neurodevelopment outcomes in neonates, infants, and young children. Two of the cohorts have also investigated the role of genetic susceptibility (PON1) in the association between pesticide exposure and adverse birth outcomes and neurodevelopmental effects. In 2008, EPA consulted the SAP on the use of these three cohort studies in mothers and their children. Details of this analysis and discussion are provided in the chlorpyrifos docket (draft Appendix D Epidemology at http://www.epa.gov/scipoly/sap/meetings/2008/091608_mtg.htm.) EPA plans to finalize the science documents reviewed by the SAP in the upcoming months.

Funded by multiple Federal Agencies, including US EPA, the three studies originate from: (1) Columbia University, NYC, (2) Mt Sinai, School of Medicine, NYC, and (3) University of California at Berkeley (Center for Health Assessment of Mothers and Children of Salinas, CHAMACOS). The first two study populations include multi-ethnic, urban low income mother-infant pairs, and the latter reflects a farm worker/agricultural worker study population[2]. The Columbia study focuses on chlorpyrifos in cord blood and the latter two studies assess the non-specific organophosphate (OP) metabolites diethyl phosphases (DEPs) and dialkyl phosphates (DAPs) in maternal urine, and link these biomarkers of exposure with associated health outcomes in children that were exposed *in utero*.

In EPA's review of the epidemiologic evidence concerning potential neurodevelopmental effects of prenatal or early postnatal chlorpyrifos and/or OP exposure, EPA noted consistency across the studies, i.e. delays in cognitive achievement, motor control, social behavior, and intelligence measures that were reported in all three prospective cohorts (Columbia, Mt. Sinai and CHAMACOS) in children 2-3 years of age. However, EPA believes the degree to which chlorpyrifos is implicated in these outcomes varies.

More recently, in April 2011, these same researchers published results indicating that *in utero* chlorpyrifos and/or OP exposure may have persistent neurodevelopmental effects for school age children up to age 7 using the Weschsler Intelligence Scale for Children-IV. Since these studies were recently published, EPA has not conducted a full evaluation of these recent publications (of the same cohort) and integrated these data with the totality of the chlorpyrifos database, but will consider these human epidemiological studies along with the available empiricial data in a full weight of evidence analysis in the final assessment. The neurodevelopmental outcomes reported for children in these epidemiology studies are qualitatively similar to the behavioral outcomes in animal studies (following gestational and/or postnatal exposures to chlorpyrifos). Some initial aspects of these three cohort studies are as follows:

- There appears to be consistency across the three children's health cohorts in both the magnitude and direction of the association between prenatal chlorpyrifos and/or OP exposure and neurodevelopment effects measured in children at several different points in time (Rauh *et al*. 2006, 2011, Engel *et al*. 2011, Eskenazi *et al*. 2007, Bouchard *et al*. 2011). The Columbia results are associated with high chlorpyrifos cord blood levels, while the CHAMACOS and Mt. Sinai teams correlated increasing levels of maternal

[2] The Mt Sinai study included inner city, black, Hispanic and white women, while the Columbia study evaluated inner city African American and Dominican. The Berkley study included homogenous Latino women from Agricultural communities.

urinary DAPs with reported mental delays in children. Table 5 shows the results from the three cohorts on mental delays in children ages 2-3.

Table 5 Prenatal OPs and Mental Delays (Bayley Mental Development Index)

Age of Child	Berkeley (log10 DAP maternal urine, Adj Beta)	Mt. Sinai (log10 DAP maternal urine, Adj Beta)	Columbia Univ. (High v. Low chlorpyrifos cord blood , Adj Beta)
6 mo.	-1.2	--	--
1 Year	-1.3	-1.0	-0.3
2 Year	-3.5*	-2.08	-1.5
3 Year	--	--	-3.3**
*p<0.05 **p<0.1			
References: Eskenazi *et al*. 2007; Engel *et al*. 2011; Rauh *et al*. 2006			

- The Columbia cohort researchers reported that prenatal chlorpyrifos (as measured in umbilical cord blood) is associated with delays in motor development, cognitive function as well as social behavioral problems including symptoms of Attention-Deficit/Hyperactivity Disorder (ADHD) (Rauh *et al*. 2006). Recent study results indicate prenatal chlorpyrifos exposure may adversely influence intelligence measures at school age (Rauh *et al*. 2011).

  The Columbia study overlapped with residential use cancellation in 2001. For children born before cancellation, high chlorpyrifos exposure in cord plasma was significantly associated with neurodevelopmental effects. In contrast, this relationship was no longer significant for newborns born after the cancellation because the blood levels dropped. Thus, this study identifies a natural experiment and indicates the effects upon neurodevelopment in children are not observed upon cessation of the exposure. As noted by the SAP in 2008, "although the data on post-ban declines in exposure are compelling, limitations must be kept in mind when using these results in the weight of evidence. The study was not designed to assess the effect of the ban, so data are essentially cross-sectional (i.e., exposures among the same women were not measured over time)."

- Both Mt. Sinai and CHAMACOS cohorts report abnormal reflexes in neonates associated with urinary maternal DEP and DAP levels. Increases in pervasive developmental disorder were reported in both the Columbia and CHAMACOS cohorts (Rauh *et al*. 2006, Engel *et al.* 2007, Young *et al.* 2005). It was acknowledged by the SAP that there are potential confounders and issues that reduce the utility of both the Mt. Sinai and Berkeley cohorts for risk assessment. For example, both studies measured non-specific OP metabolites in urine but not chlorpyrifos. The Berkeley study has the least relevance to chlorpyrifos risk assessment because only a small percentage (10%) of the pesticides applied in Salinas Valley are chlorpyrifos therefore, chlorpyrifos would make only a small contribution to the non-specific metabolites measured in the study and study

outcomes, although this assumption has not been verified. As such, it is difficult to ascribe the effects seen to chlorpyrifos, in particular, rather than OPs in general. Nevertheless, the SAP advised that "although Mt. Sinai and Berkely cohorts are less specific than the Columbia Study, they support the overall findings of the latter" (pg 43 SAP report)

- Although CHAMACOS and Mt. Sinai have focused on OP (i.e., DAPs) exposure and not chlorpyrifos, *per* s*e, the SAP encourag*ed the Agency to consider the results of all three cohorts together with an emphasis on Columbia University for the chlorpyrifos assessment since as there are "more similarities than discrepancies across them" (p. 43, FIFRA SAP, 2008). But the SAP also noted that it cannot be stated that chlorpyrifos is the sole contributor to the observed outcomes; exposures to all three ACh-E inhibiting insecticides may act in combination to produce the observed effects. Although the authors of the Columbia studies have attempted to isolate the effects that would be associated with chlorpyrifos, the Panel noted it is difficult to quantify the contribution of other neurotoxic compounds in such simultaneous exposures. (See follow up analysis by Whyatt and Rauh (2010) that evaluated a joint effects model and concluded chlorpyrifos and not diazinon or propoxur were associated with the outcomes).

There are several strengths of the epidemiological database associating prenatal chlorpyrifos and other OP exposure with neurodevelopment effects in neonates, infants, young children and school aged children. Specifically, the measurement of the neurodevelopmental outcomes (e.g., Brazelton index, Bayley scale, and the Weschlar Intelligence Scale) are accepted valid and reliable measurement tools in clinical and epidemiologic research. In addition, the use of biological markers of exposure [i.e., cord blood concentration of chlorpyrifos or maternal urinary DEPs and DAPs], are more accurate and reliable measures of prenatal exposure than other forms of exposure assessment such as self-report questionnaire. Notably, the exposure measurements (biomonitoring and/or personal air monitoring) were well coordinated with the exposure period of interest (third trimester for birth outcomes)[3]. The Columbia study measured chlorpyrifos in umbilical cord blood at delivery, and maternal blood measurements during pregnancy and delivery. The researchers in each of these cohorts utilized robust and appropriate statistical analysis methods to model the exposure-response association including adjustment for potentially confounding variables.

All three cohort studies have limitations that include multiple chemical exposures and exposure to other organophosphates. The exposure classification is based on maternal spot urinary samples for the Mt. Sinai and CHAMACOS studies and maternal and cord blood samples in the Columbia Study that may not necessarily represent total chlorpyrifos or OP exposure throughout pregnancy because these pesticides have short half-lives. However, the prevalence of exposure among these cohorts based upon a one-time sample indicates the total exposure may be greater than measured (exposure measurement error likely exists), and results of meconium analyses in the Columbia cohort indicate chlorpyrifos exposure occurred throughout pregnancy. Meconium is considered to be an integrative measure of exposure throughout pregnancy. In addition, the Mt. Sinai and CHAMACOS studies associate increased maternal urinary DAP levels with increased mental delays in children. DAP metabolites are non-specific metabolites that result

[3] The third trimester is a critical window of exposure for brain development.

from several OP pesticides, so it is difficult to determine which OP compound may be contributing most to the adverse findings.

While neurodevelopment deficits may be multifactor in origins, these children are from low income multi-ethnic populations and urban neighborhoods and may experience other exposures that may also influence neurodevelopmental outcomes. These may include health disparities that compound pesticide exposure such as poor diet, low access to health care, socioeconomic issues associated with low income and low education, as well as exposure to urban air pollutants. In addition, a recent follow-up publication for the Columbia cohort reported that neighborhood context and chlorpyrifos exposure were independently associated with neurodevelopment (Lovasi *et al*. 2010). Additional analyses were performed to consider neighborhood characteristics, economic deprivation, neighborhood poverty, and maternal hardship to help explain the variation in early childhood psychomotor and mental development. Adjustment for these factors did not change the chlorpyrifos and child neurodevelopment association (Lovasi *et al*. 2010).

The SAP recommended that the epidemiology and direct dosing human studies should not be considered quantitatively for PoDs, but can be used for hazard characterization. The SAP concluded that the results of the three cohort studies (Columbia University, Mt. Sinai Hospital, and the University of California at Berkeley) in concert with the animal studies indicate that "maternal chlorpyrifos exposure would likely be associated with adverse neurodevelopmental outcomes in humans". However, they indicated that exposure to multiple cholinesterase-inhibiting pesticides or other neurotoxicants might result in additive or interactive effects[4]. The Columbia study was considered the most epidemiologically-sound and robust because it measured chlorpyrifos in maternal and cord blood (rather than non-specific metabolites). Challenges in the interpretation of the Mt. Sinai and Berkeley studies include use of non-specific measures of pesticide exposure, based on OP and carbamate metabolites, rather than chlorpyrifos, reduce their utility in a quantitative context for the chlorpyrifos risk assessment.

The Panel recommended that the Agency conduct a full weight of evidence evaluation for the neurodevelopmental outcomes. Such an exercise requires explicit consideration of criteria such as strength, consistency, specificity related to chlorpyrifos or to its anticholinesterase effects common to OPs as a whole, dose-response, temporal concordance and biological plausibility in a framework analysis similar to that which is conducted currently for hypothesized modes of action. This allows comparative analysis across assessments of consistency of weight of evidence determinations. The weight of evidence analysis might increase confidence in this case and potentially identify additional relevant analyses to address uncertainties such as the role of other pesticides in the observed associations.

The SAP recommended that the Columbia University cohort study could be used to determine bounding values for the levels of chlorpyrifos that might cause a measurable effect. In a similar way, data from the other epidemiological studies may also be used in risk assessment. The use of a PBPK model would enable estimation of an exposure dose metric for multiple sources of

[4] Follow up analyses conducted by the Columbia Researchers (Whyatt and Rauh 2010) show that the adverse impact of chlorpyrifos on cognitive development is not due to other anticholinesterase pesticides (diazinon or propoxur exposure).

exposure, e.g., air, food, water. The panel agreed that the blood and urine data in the deliberate human dosing studies are important in interpreting the epidemiology and biomonitoring studies.

The Agency intends to carefully consider the strengths and limitations of the epidemiology studies along with the available empirical data in a full weight of evidence analysis in the final assessment.

4.4.2 Agricultural Health Study (AHS)

For chlorpyrifos, in addition to the guideline carcinogenicity studies, epidemiological data is available from an Agricultural Health Study (AHS). The Agency has reviewed the AHS report and concluded that while the AHS investigations currently published were hypothesis-generating in nature, initial strength and consistency in the findings for lung cancer and colorectal cancer are notable, and warrant further follow-up and additional research. Preliminary associations with breast and prostate cancer are weak, but also warrant monitoring the literature for additional publications on this association. There is no compelling evidence of an association with other cancer sites including pancreatic cancer, melanoma, brain, esophageal, kidney, all lymphohematopoietic cancers combined and NHL, leukemia, and multiple myeloma (C. Christensen, 6/16/11, D388167).

4.5 New Developments since the 2008 SAP

In 2008, the Agency held a SAP meeting (SAP 2008) to discuss the more recent and extensive research on various aspects of chlorpyrifos including its neurological effects in animals and humans following gestational and post-natal exposures, its pharmacokinetics, and mechanism of action. Details can be found in the Chlorpyrifos Final SAP Report at on the Scientific Advisory Panel website (http://www.epa.gov/scipoly/sap/meetings/2008/091608_mtg.htm). Many of the key recommendations have been incorporated into this preliminary risk assessment.

Since the 2008 SAP the agency has reviewed new data and analyses, and held additional public meetings to discuss specific aspects of chlorpyrifos including:

- Evaluated new toxicity data
- Consulted the Human Studies Review Board (HSRB)
- Conducted follow up analysis on the Columbia Epidemiology Study
- Consulted the SAP in 2011 on PBPK modeling

New Toxicity Data: Since 2008, the Agency has reviewed an acute and repeat special non-guideline CCA study (Marty and Andrus 2010, MRID No.: 48139301, HED TXR No. 0055409), an acute inhalation study (2010, MRID 48139303), and immunotoxicity study. The CCA study was conducted to compare the relative toxicity of chlorpyrifos and chlorpyrifos oxon in both juvenile (PND11 pups) and adult rats based on ChE inhibition. Both acute (single) dosing and a repeat 11 day exposure scenario were evaluated for chlorpyrifos and chlorpyrifos oxon. Although the study identified both NOAELs and LOAELs for plasma, RBC and brain ChE inhibition, the Agency used these data to conduct BMD analysis (see Appendix E for BMD results). An acute rat inhalation study was evaluated that identified lung and RBC ChE

inhibition as the most sensitive effect at the lowest dose tested of 3.7 mg/m^3. A BMD analysis was attempted but did not provide high confidence results due to the nature of the dose response data. The Agency estimated a HEC of 0.62 mg/m^3 from this study for use in a preliminary assessment of bystander (field volatilization) exposures. In addition, the Agency also reviewed a guideline immunotoxicity study that did not identify adverse effects on the immune system at the highest dose tested.

HSRB: In June 2009, the Agency consulted the Human Studies Review Board (HSRB) (June 24-25, 2009; http://www.epa.gov/hsrb/jun-24-25-2009-public-meeting.htm) regarding deliberate dosing studies in adult (non-pregnant) humans that measure ChE activity and urinary and/or blood levels of chlorpyrifos and/or its metabolites. Nolan *et al* (1982; MRID 124144) was found to be scientifically and ethically conducted by HSRB and EPA also determined that the study was ethically acceptable. Kisicki *et al* (1999), (MRID 44811002) was found to be scientifically (and ethically) conducted by HSRB. However, EPA ethics review had determined that this study did not meet the Agency's ethical standards and therefore concluded that "EPA is forbidden by 40 CFR §26.1704 to rely on the Kisicki *et al.* study, MRID 44811002, in actions taken under FIFRA or §408 of FFDCA…." (J.Carley memo dated 5/29/09; http://www.epa.gov/hsrb/files/1d6-ethics-rvw-kisicki-etal-060109.pdf). Thus, the Kisicki data have not been used in the preliminary chlorpyrifos human health risk assessment (Appendix D).

Epidemiology. The SAP recommended a number of follow up analyses for the Columbia cohort. Importantly, the panel advised that "it would be useful to examine the results of a statistical analysis that includes all three ChE-inhibiting insecticides in the analysis model as dichotomous variables (above or below the LOD) in combination with continuous measurements for these variables." Follow up analyses conducted by the Columbia Researchers (Whyatt and Rauh 2010) show that the adverse impact of chlorpyrifos on cognitive development is not due to other anticholinesterase pesticides (diazinon or propoxur exposure), and these analyses do not reduce the chlorpyrifos effect for any of the 3-year outcomes for mental or psychomotor delays. The Columbia researchers also addressed a number of other questions raised by the SAP, and they do not affect to conclusions of their publications.

PBPK Modeling. At the 2008 SAP, the panel recommended that the Agency consider the potential for using PBPK modeling in human health risk assessment for chlorpyrifos. PBPK models have been published for chlorpyrifos (Timchalk *et al*, 2002a, 2007; Rigas *et al*, 2001; Knaak, *et al*, 2004; Georgopoulos *et al*, 2008). The model(s) developed by Dr. Charles Timchalk and co-workers at of Pacific Northwest National Laboratory has been the most extensively developed. The Timchalk model was first published in 2002 as an adult rat and human model (Timchalk *et al*., 2002a) and has been updated as more data have become available (Poet *et al*. 2003; Poet *et al*. 2004; Slikker *et al*. 2005; Timchalk *et al*. 2002b; Timchalk *et al*. 2003; Timchalk *et al*. 2005; Lowe *et al*., 2009). Timchalk *et al*. (2007) published a similar model for juvenile rats that incorporated age-dependent changes. Recently, Dow AgroSciences, Dow Chemical and Dr. Timchalk and co-workers have worked collaboratively to improve the chlorpyrifos PBPK model by considering more lifestages (6 month and 3 year olds) and evaluating population variability. The PBPK model has also been linked to a probabilistic exposure model as an approach to estimate population risk. The status of these efforts was considered by the FIFRA SAP in February 2011. At the 2011 meeting, the Panel was

supportive of the overall concepts of linking PBPK models to probabilistic exposure models and of estimating population risk; however, the Panel pointed out limitations to the current effort that precludes its use at the present time. For example, the PBPK models do not simulate pregnancy and thus do not estimate *in utero* exposure to the fetus. In addition, the model only considers oral exposure (with a particular focus on food exposure) but inhalation exposure can be an important route of exposure for chlorpyrifos for both bystanders from field volatilization and to pesticide applicators.

In addition, the Agency is aware of another PBPK modeling effort led by Dr. Dale Hattis of Clark University in collaboration with the Columbia University epidemiology team. This PBPK model may, in the future, be useful in clarifying the exposure concentrations that correspond to the chlorpyrifos levels in umbilical cord blood associated with statistically significant adverse effects on fetal growth and child neurocognitive development.

4.6 Safety factor for Infants and Children (FQPA Safety Factor)

Due to the preliminary nature of this assessment the Agency is presenting assessments reflecting both the retention of the 10X FQPA Safety Factor as in the June 2000 chlorpyrifos risk assessment (USEPA 2000), and a proposal to reduce the FQPA SF to 1X based on more recently available ChE toxicity studies and analyses. In those instances where the Agency has proposed to reduce the FQPA SF to 1x, the Agency believes data are supportive of this proposal. EPA is conducting on-going analyses of newly published literature studies on a variety of challenging scientific issues such as high to low dose extrapolation, animal to human extrapolation, evaluation of the non-cholinergic literature, and interpretation of epidemiology studies in the context of assessing human health risk to chlorpyrifos. EPA will continue to evaluate all the data/studies to determine the appropriate FQPA SF for future chlorpyrifos risk assessments.

4.6.1 Completeness of the Toxicology Database

The toxicological database for chlorpyrifos is extensive and is adequate to support the registration review (Section 4.1 above). The toxicity data base includes the standard battery of guideline studies as well as special studies conducted by the registrant. The scientific literature on chlorpyrifos includes data from many sources, in animals and humans, and some studies with atypical study designs and relatively new assessment techniques. Sources of human information include deliberate dosing studies, epidemiology studies, and metabolism studies (*in vitro* and *in vivo*). There are a variety of laboratory animal studies evaluating a broad range of doses for multiple sensitive lifestages. In addition, these studies consider different durations of exposure (acute, short-, intermediate-term and chronic) and relevant routes of exposure (oral, dermal, and inhalation), different laboratory animal species, reproductive and developmental toxicity, neurotoxicity, developmental neurotoxicity (DNT), new acute and repeat dose comparative cholinesterase assays (CCA) for both chlorpyrifos and chlorpyrifos oxon, a special acute inhalation toxicity study and a required immunotoxicity study.

4.6.2 Key Scientific Information Available to Inform the Safety Factor

The mode of action (MOA) for organophosphate pesticides, like chlorpyrifos, leading to neurotoxicity is inhibition of ChE (See Section 4.3). Concerns regarding the potential hazards to children associated with post-natal exposure to chlorpyrifos and other organophosphate pesticides is derived from data showing that the young have increased sensitivity to ChE inhibition (i.e., the young will have more inhibition than the adult when given the same administered dose). Specific to chlorpyrifos, several toxicity studies with chlorpyrifos and its oxon, including the new CCA study, show that juvenile rat pups are more sensitive to acute chlorpyrifos exposure than adult rats for ChE inhibition. The increased sensitivity of the young from acute exposure is likely attributed to a reduced capacity to detoxify chlorpyrifos in juvenile animals. There is a clear age-dependant sensitivity which diminishes as the pups mature; this pattern is likely reflective of the metabolic processes which rapidly mature in the rat pup. The SAP concurred with the Agency that juveniles are more sensitive than adults to ChE inhibition following acute exposures, but not necessarily for repeated exposures.

In addition to effects on ChE inhibition, there is concern that the young have a unique susceptibility to chlorpyrifos due to its effects on the developing brain. A number of animal toxicity studies examining the effects of chlorpyrifos in the developing brain indicate that gestational and/or early postnatal exposure to chlorpyrifos can lead to neurochemical and behavioral alterations that persist into adulthood (Gupta *et al*, 2011, USEPA 2008 draft hazard and dose response issue paper), including long-term neurobehavioral changes in motor and cognitive behaviors (Aldridge *et al*., 2005c; Levin *et al*., 2001, 2002, Ricceri *et al*., 2003, 2006 Johnson *et al* 2009). However, these findings generally occurred at doses that are often associated with ChE inhibition (> 1 mg/kg/day; the 10% BMD for brain ChE inhibition is about 1.4 mg/kg/day for acute and 0.6-0.8 mg/kg/day for repeated exposure to the PND11 pups in the CCA study) and thus at doses higher than the new oral PoDs being used in this preliminary assessment. In addition, most of the literature studies evaluating non-cholinergic mechanisms and behavioral outcomes provide insufficient information to establish a dose-response due to testing one or two treatment groups and or poor dose selection.

In addition, many *in vitro* literature studies and the guideline developmental neurotoxicity (DNT) study are supportive of the possibility that chlorpyrifos exposure may affect brain development (e.g., altered synaptic development, alterations in DNA, RNA, and protein synthesis, inhibition of mitosis and mitotic figures, and disruption of the structural architecture of the brain) (USEPA 2000b). Qualitative susceptibility between adult rats and their offspring was seen in the guideline DNT study (cholinesterase inhibition in dams at ≥0.3 mg/kg/day versus structural effects on developing brain of the PND 66 offspring at ≥ 1 mg/kg/day) (Hoberman 1998a,b, HED Review D254907). Although an apparent increased qualitative susceptibility was observed in the DNT study, the SAP panel indicated that adult brain morphometric measurements of the cortical regions displayed about 10% variability, a level expected to be within normal variability for such crude measurements. The SAP also advised that histological assessment and morphometric measurements used in the DNT have significant limitations and cannot detect changes in the network organization of the brain or possible other changes. Unbiased stereology should be used for determining cell number and tissue volume. Thus, it is

possible that the Agency's current interpretation of the PND 66 offspring morphometric data in the DNT study may be revisited pending additional information and analysis.

The mode(s) of action associated with the effects on the developing brain are still not known. However, over the last 15 years, biologically plausible hypotheses for chlorpyrifos have been proposed by researchers. These include effects on signaling pathways (Slotkin, 2006), a morphogenic role of ChE effect the structure of the brain (Brimijoin and Koenigsberger, 1999 and Bigbee *et al*, 1999; Yang *et al*, 2008) and recently a reduction in axonal transport mediated through impaired tubulin polymerization (Prendergast *et al*, 2007; Grigoryan *et al*, 2008; Grigoryan *et al* 2009; Grigoryan and Lockridge, 2009; Jiang *et al*, 2010) Although multiple mechanisms have been proposed, a coherent mode of action with supportable key events, particularly with regard to dose-response and temporal concordance, has not yet been elucidated. The Agency may consider additional studies on possible non-cholinergic modes of action in the future, including those cited by Eaton *et al*. (2008), as well as studies reported since that time. The Agency is currently updating its evaluation of the non-cholinerigic literature.

The epidemiological data (Columbia University, Mt. Sinai, and CHAMACOS) do not provide sufficiently robust dose-response information for derivation of a quantitative measure of human risk at this time. The FIFRA SAP (2008) concurred with the proposal to use these studies for qualitatively supporting the risk assessment but not for use in quantitative extrapolation. The SAP pointed out some uncertainties remain the preclude the use of the epidemiology studies in quantitative risk assessment: 1) only measuring biomarkers (3rd trimester maternal, cord blood, meconium) at 1-point in time; 2) the studies do not information as to critical window of effect; and 3) they cannot exclude possibility that effect seen due to chlorpyrifos in combination with other pesticides (additive, multiplicative effect). Similar to many other epidemiology studies, these studies have not measured air exposures, urinary or blood metabolites at or near the timing of pesticide applications. However, the FIFRA SAP said these are high quality studies and supported their use as qualitative information to support the neurodevelopmental toxicity of chlorpyrifos following gestational and/or postnatal exposures since there are "more similarities than discrepancies across them". The Columbia study was considered the most epidemiologically-sound and robust because it measured chlorpyrifos in maternal and cord blood (rather than non-specific metabolites). Qualitative similarities between the findings in animal behavioral studies and in the epidemiology studies include impaired cognition, abnormal motor development, and altered social development in children, possibly persisting into school-age (7 years) (Rauh *et al*. 2006, 2011, Engel *et al*. 2011, Eskenazi *et al*. 2007, Bouchard *et al*. 2011).

Inhibition of ChE is the most sensitive endpoint measured in dose response studies in any animal species and in humans, regardless of route or duration of exposure. As such, ChE inhibition has been and continues to be the endpoint used for human health risk assessment for OPs, including chlorpyrifos. In the 2000 risk assessment (EPA 2000a), EPA used a weight of the evidence approach with ChE data from multiple adult laboratory animal studies and multiple species (rat, dog) as the basis of the PoD for all durations and routes of exposure. Since then, numerous new studies in juvenile animals have become available, notably acute and 11 day repeated dosing CCA studies for chlorpyrifos and its oxon. As shown in the draft EPA 2008 issue paper, and draft Appendix C (Mode of Action: Inhibition of Cholinesterase at http://www.epa.gov/scipoly/sap/meetings/2008/091608_mtg.htm), there are extensive ChE data

in juvenile rats ranging from PND1-PND33. EPA updated the oral PoDs based on the most sensitive lifestage(s) relevant to direct oral human exposures. Rat pups younger than approximately PND10 are more physiologically similar to human fetuses *in utero*. As such, the Agency has focused its quantitative dose response efforts on rats ages PND11 and older for oral exposures using BMD modeling for 10% RBC ChE inhibition.

EPA is still evaluating the latest epidemiology (Rauh *et al*. 2011, Engel *et al*. 2011, Bouchard *et al*. 2011) and PBPK data and modeling efforts by Dow AgroSciences and Dr. Dale Hattis to be more explicit about uncertainty and variability, and to have a more accurate picture of the doses at which adverse effects might happen in humans and animals. Thus, the PoDs proposed in this preliminary assessment, and associated uncertainty/FQPA factors, could change.

4.6.3 Application of the FQPA Safety Factor for the Preliminary Risk Assessment

In this preliminary assessment, EPA is presenting the risk estimates using both the PoDs and the 10X FQPA SF retained in 2000, and oral PoDs based on new CCA study providing a sensitive endpoint and lifestage with a 1X FQPA and updated quantitative tools (BMD modeling). EPA is continuing to conduct ongoing analysis to ensure a sound scientific basis for the appropriate factor.

2000 Risk Assessment. In the June 2000 chlorpyrifos risk assessment, the FQPA safety factor was retained at 10X for the protection of infants and children to exposure resulting from chlorpyrifos (USEPA 2000a, b, c). At that time, the Agency used PoDs based on NOAELs for plasma and/or RBC ChE inhibition from adult data in laboratory animals and recommended that a 10X safety factor be retained for chlorpyrifos due to:

(1) Increased sensitivity and susceptibility was not only a high dose phenomenon since:

- Increased sensitivity to ChE inhibition following a single oral exposure to neonates was seen at substantially lower doses in PND 7 pups compared to adults (i.e., < 1.5 mg/kg/day) (Zheng *et al*. 2000); and

- A clear qualitative difference in response (i.e., susceptibility) between adult rats and their offspring was demonstrated in the developmental neurotoxicity (DNT) study (cholinesterase inhibition in dams versus structural effects on developing brain of the offspring) (Hoberman 1998a,b, HED Review D254907).

(2) New data available in the literature at the time of the 2000 risk assessment also gave rise to uncertainties such as:

- The suggestion that the inhibition of cholinesterase may not be essential for adverse effects on brain development (see EPA literature review in USEPA 2000b) [5]; and

[5] The mechanism(s) of action for the chlorpyrifos-induced changes (e.g., macromolecular synthesis, cell signaling) is/are unclear. However, given that these effects can be found after intracisternal injection of chlorpyrifos, with in

- The lack of an offspring NOAEL in the DNT based upon structural alterations in brain development as the toxicity endpoint of concern.

2011 Preliminary Risk Assessment:

As noted previously, EPA solicited comment from the SAP in 2008 on extensive research on various toxicological aspects of chlorpyrifos, including its neurological effects in animals and humans following gestational and post-natal exposures, its pharmacokinetics, and mechanism of action. Details can be found in the Chlorpyrifos Final SAP Report at (http://www.epa.gov/scipoly/sap/meetings/2008/091608_mtg.htm). The SAP made a number of recommendations on updating the PoDs which are incorporated into the current preliminary risk assessment. Key SAP recommendations included here are: take into account all sensitive life stages; and use benchmark dose modeling instead of the NOAEL/ LOAEL approach when possible.

Since the 2008 SAP meeting, EPA has received and reviewed a new acute and repeat CCA study for both chlorpyrifos and chlorpyrifos oxon (Marty and Andrus 2010). This study is considered high quality, and provides reliable measures of blood and brain ChE at the time of peak effect (6-8 hours post-dosing), uses 4-6 doses and use a wide range of doses. BMD analyses were conducted for both RBC and brain ChE inhibition for this CCA study, in addition to many other literature and registrant studies for both acute and repeat exposure (Betancourt and Carr 2004, Zheng *et al*. 2000, Moser *et al*. 2006, Timchalk *et al*. 2006, Mattsson *et al* 1998, Hoberman 1998a,b) (see Appendix E for BMD analyses). These studies were all considered for endpoint selection. The RBC ChE inhibition BMD for acute chlorpyrifos exposure to PND11 pups administered via milk provides the lowest oral PoD in the entire database of the relevant studies[6] and thus was selected as the new acute oral PoD (Marty and Andrus 2010). The chronic PoD was based on data for pregnant rats in the DNT study (Hoberman 1998a,b), which resulted in the most sensitive PoD, and was also the basis of the 2000 cPoD, along with 4 other studies. For chlorpyrifos oxon, the CCA results were used to develop acute and chronic PoDs based on BMD analysis for RBC ChE inhibition.

Like other OPs, ChE inhibition provides the most sensitive dose-response data for chlorpyrifos. As a result, the focus of the 2011 preliminary risk assessment is on the cholinesterase inhibiting potential of chlorpyrifos. Consistent with this focus, EPA has evaluated the extensive database of ChE data for multiple lifestages and has selected the most sensitive studies which use ages relevant to human exposure. There are no residual uncertainties in the exposure database. The dietary risk assessment is conservative and is not expected to underestimate dietary exposure to chlorpyrifos and chlorpyrifos oxon. Similar to risk assessments conducted for other ChE-inhibiting pesticides where juvenile pups provide the PoDs for risk assessment, the FQPA SF is being reduced to 1X for this preliminary assessment for acute and chronic oral exposure, in addition to dermal and inhalation exposure to chlorpyrifos. The repeated inhalation PoDs are

vitro TCP treatment, and in vitro PC12 cell cultures with limited capability to activate chlorpyrifos to its ChE-inhibiting oxon, raised the issue of whether these effects can occur independent of cholinesterase inhibition.

[6] Data for pups less than PND10 were not considered relevant for direct human exposure, since this represents the human fetal stage

considered protective of sensitive lifestages (pregnant rats). For acute inhalation exposure, a 10X FQPA database uncertainty factor is retained to account for LOAEL to NOAEL extrapolation.

For chlorpyrifos oxon, the Agency proposes to reduce the FQPA SF to a 1X for acute and chronic exposure because the acute PoD is based on a sensitive lifestage (juvenile pups) in the CCA study and the chronic is based on the lowest BMDL available in the CCA study.

Table 6 Application of FQPA SF Comparison of 2000 and 2011 Risk Assessment for Chlorpyrifos

	Point of Departure (mg/kg/day)	
	2000 10X FQPA SF (a)	**Proposed 1X FQPA SF (b)**
Acute PoD	0.5 (mg/kg/day;NOAEL)	0.36 ($BMDL_{10}$)
Chronic PoD	0.03 (NOAEL)	0.03 ($BMDL_{10}$)
Incidental oral	0.5 (NOAEL)	ST: 0.1 ($BMDL_{10}$) IT: 0.03 ($BMDL_{10}$)
Dermal	ST: 5 (NOAEL) IT: 0.03 (NOAEL)	ST/IT: 5 (NOAEL) (c)
Inhalation	ST/IT: 0.1 (NOAEL)	Acute: 0.62 mg/m3 (HEC, LOAEL) (d) ST/IT: 0.0057 mg/m3 (HEC, NOAEL 24 hr residential) (e)

$BMDL_{10}$= benchmark dose lower confidence limit for 10% RBC ChE inhibition
HEC= human equivalent concentration; ST/IT= short and intermediate-term
ST= short –term; IT= intermediate- term

(a) A 10X FQPA SF is retained to the PoDs from the 2000 risk assessment because these are based on adult animal data.
(b) Except where noted, 1X FQPA SF is proposed for 2011 PoDs because they are based on the most sensitive lifestage (i.e., PND 11 and pregnant animals).
(c) For dermal exposure, a 1X FQPA SF is proposed because of the conservative nature of the PoD that is based rat data. Rats have more permeable skin than humans.
(d) For acute inhalation exposure, a 10X FQPA database uncertainty factor is applied to account for LOAEL to NOAEL extrapolation.
(e) For repeated inhalation exposure, a 1X FQPA SF is applied because the PoD is based on route-specific 90 day inhalation studies, and a LOAEL from the DNT study to protect pregnant females from RBC CHE inhibition (LOAEL of 0.3 mg/kg/day)

Table 7 Application of FQPA SF in Risk Assessment for Chlorpyrifos Oxon

	Point of Departure (mg/kg/day)	
	Proposed 10X FQPA SF	**Proposed 1X FQPA SF**
Acute PoD	--	0.05 (BMDL10) (a)
Chronic PoD	--	0.011 (BMDL10) (b)
Dermal	Not applicable	
Inhalation	Not applicable	

(a) 1X FQPA SF proposed since the aPoD is based on sensitive lifestage (juvenile animals).
(b) 1X FQPA database UF because the most sensitive PoD was selected (in 11 day CCA study using adults), that is protective of juvenile rats.

Next Steps in the FQPA SF Analysis:

Analyses are ongoing to fully examine recently proposed biologically plausible modes of action which could lead to effects on the developing brain and to consider these new data in light of the epidemiology studies in mothers and children. As such, the Agency continues to analyze and integrate the animal and human epidemiology data to ensure that a sound scientific analysis around key scientific areas such as high to low dose extrapolation, animal to human extrapolation, and interpretation of epidemiology studies in the context of assessing human health risk to chlorpyrifos. These ongoing analyses will ensure that the PoDs and UFs in this preliminary assessment are human health protective for neurodevelopmental toxicity that may arise from pre- or postnatal exposure. The Agency's final FQPA determination will be based on a full scientific weight of evidence approach that considers the best available science and integrates all key lines of evidence, from empirical animal toxicology to observational human epidemiology studies, in an integrated framework analysis and will transparently address and clearly characterize the strength of the evidence and areas of remaining uncertainty and variability. The Agency plans to conduct a full weight of evidence evaluation integrating the epidemiology studies with the experimental toxicology studies for the neurodevelopmental outcomes using the *Draft Framework for Incorporating Epidemiologic and Human Incidence Data in Human Health Risk Assessment*[7], which was reviewed favorably by the FIFRA SAP in February, 2010 (USEPA, 2010) Such a weight of evidence analysis requires explicit consideration of such criteria as strength, consistency, specificity, dose response, temporal concordance and biological plausibility.

This final determination will also consider the 2008 SAP comments and the public comments received on this preliminary risk assessment. Thus, the intra-, and inter-species UFs along with the FQPA SF could change with these additional analyses. The Agency is seeking comment on the proposed FQPA SF for the final chlorpyrifos risk assessment.

4.7 Toxicity Endpoint and Point of Departure Selections

4.7.1 Dose-Response Assessment

Table 8 summarizes the chlorpyrifos toxicity endpoints and PoDs selected from a re-evaluation of the database (including data submitted since the 2002 IRED/2006 RED). Based on the results of benchmark dose (BMD) analyses and weight of the evidence (WOE) consideration of all quality and reliable data, the most sensitive compartment (i.e., RBC, lung or brain) from the most sensitive sex in both juvenile (> PND11) and adult rats were identified and used for endpoint selection and PoD determination for the following exposure scenarios. Descriptions of the primary toxicity studies used for selecting toxicity endpoints and points of departure for various exposure scenarios are presented in Appendix A of this document. The description and results of the BMD analyses can be found in Appendix E. The SAP recommended selecting PoDs based on BMD analysis for RBC ChE inhibition for the most sensitive lifestages (i.e., pup and pregnant females). The Panel supported the continued use of route-specific data for dermal and inhalation, but advised EPA to take into account sensitive lifestages since these studies are based

[7] http://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPP-2009-0851-0004

on adult non-pregnant animals. Most of the panel believed that the PoDs based on ChE inhibition would be protective of the developing brain from low level *in utero* exposures, although there was no consensus. The Panel encouraged the Agency to address uncertainties including lack of information on an MOA for behavioral effects and *in vivo* and *in vitro* studies that indicate non-cholinergic MOA are likely to be involved in neurodevelopment and behavioral effects. The Agency is conducting ongoing analyses to ensure that the PoDs and UFs in this preliminary assessment are human health protective for neurodevelopmental toxicity that may arise from pre- or postnatal exposure.

Consistent with risk assessment on other OP and NMCs compounds, the Agency has used a benchmark response (BMR) level of 10% and has thus calculated BMD_{10}s and $BMDL_{10}$s. The BMD_{10} is the estimated dose where ChE is inhibited by 10% compared to background. The $BMDL_{10}$ is the lower confidence bound on the BMD_{10}. Extensive analyses conducted as part of the OP cumulative risk assessment (USEPA 2002) have demonstrated that 10% is a level that can be reliably measured in the majority of rat toxicity studies, and is generally at or near the limit of sensitivity for discerning a statistically significant decrease in ChE activity across the brain compartment and is a response level close to the background brain ChE level. The Agency uses the BMDL, not the BMD, for use as the PoD since the BMDL accounts for variability of the data.

The Agency has not performed BMD analysis on studies evaluating the effect of chlorpyrifos on the developing brain as these do not provide dose response data amenable to BMD modeling analysis. Specifically, these studies, in general, may include only a single dose at a particular age, do not report graded responses (i.e., all or nothing effect), and/or show non-monotonic dose response curves (e.g., response goes up then down). For these studies, the Agency simply considered the doses used.

Acute Dietary (all populations)

Two high quality studies were identified in the re-evaluation of the toxicological database; these include the new CCA rat study (MRID 48139301) and Moser *et al*. (2006) in male PND17 rats. Results of BMD analyses of these well-conducted studies revealed that male and female pup RBC ChE and male whole blood ChE inhibition were the most sensitive endpoints and appropriate as a PoD for the acute dietary (all populations) exposure scenario. A $BMDL_{10}$ of 0.36 mg/kg/day associated with RBC ChE inhibition in male and female rat pups exposed to chlorpyrifos in milk (new CCA study) was selected as a suitable PoD with support from the $BMDL_{10}$ of 0.4 mg/kg from Moser *et al.* (2006). The published studies of Zheng *et al*. (2000) and Timchalk *et al*. (2006) provide additional support for the acute PoD.

An uncertainty factor of 100X (10X to account for interspecies extrapolation and 10X for intraspecies variation) is applied to the $BMDL_{10}$ to obtain an aRfD of 0.0036 mg/kg/day. Based on the proposed FQPA safety factor of 1, the acute population adjusted dose (aPAD) is 0.0036 mg/kg/day.

Chronic Dietary (all populations)

A chronic PoD of 0.03 mg/kg/day ($BMDL_{10}$) was selected from pregnant (GD6-20) rats exposed to chlorpyrifos in the developmental neurotoxicity study (MRID 44556901, Hoberman *et al*. 1998a,b) on the basis of inhibition of RBC ChE in pregnant dams. This PoD was supported by a WOE evaluation of other studies including an oral gavage study in pregnant (GD6-LD10) rats (MRID 44648101) and the new CCA study. An uncertainty factor of 100X (10X to account for interspecies extrapolation and 10X for intraspecies variation) was applied to the $BMDL_{10}$ to obtain a cRfD of 0.0003 mg/kg/day. Based on the proposed FQPA safety factor of 1, the chronic population adjusted dose (cPAD) is 0.0003 mg/kg/day.

Incidental Oral

For short-term incidental oral exposure scenario, the results of the 11 day repeat phase of the new oral CCA study (MRID 48139301) indicated inhibition of RBC ChE in male PND11 rats as the most sensitive endpoint. A $BMDL_{10}$ of 0.1 mg/kg/day was derived from a BMD analysis of the dose- response data. For intermediate-term incidental oral exposure scenarios a $BMDL_{10}$ of 0.03 mg/kg/day was identified (see chronic dietary PoD selection above).

A total uncertainty factor of 100X is appropriate for incidental oral exposures [10X for interspecies extrapolation, 10X for intraspecies variation and a 1X FQPA safety factor].

Dermal

A short-/intermediate-term dermal PoD was selected from a 21-day dermal toxicity study (MRID 40972801) in rats based on plasma and red blood cell ChE inhibition (NOAEL = 5 mg/kg/day). The use of the 21-day dermal toxicity study is appropriate for durations up to 6 months as it is expected that steady state ChE inhibition would have been reached by approximately 21 days of dermal exposure. The Agency has previously shown (USEPA, 2001; preliminary organophosphate cumulative risk assessment) that at or near 3-4 weeks of exposure the degree of inhibition following repeated dosing with OPs does not change with increasing duration but instead remains approximately the same.

For comparison to biomonitoring data in the risk assessment, which evaluates total exposure from oral, dermal and inhalation routes (in terms of absorbed dose), the 21-day rat dermal study is used with an adjustment for 3% dermal absorption to convert the NOAEL of 5 mg/kg/day resulting from topically applied chlorpyrifos to an internal absorbed NOAEL = 0.15 mg/kg/day. The dermal absorption factor of 3% was estimated based on the ratio of the oral LOAEL of 0.3 mg/kg/day from the rat developmental neurotoxicity study (MRIDs 44556901, 44661001) to the dermal LOAEL of 10 mg/kg/day from the 21-day rat dermal study (MRID 40972801) for plasma and red blood cell cholinesterase inhibition. This absorption factor is comparable to the dermal absorption (minimum 1-3%) estimated from human data in Nolan *et al*. (1982, MRID 00249203) by back-calculating chlorpyrifos exposure based on urinary levels of TCP. Most of the absorbed dose in the worker biomonitoring study is the result of dermal exposure.

A total uncertainty factor of 100X is appropriate for dermal exposures [10X for interspecies extrapolation, 10X for intraspecies variation and a 1X FQPA safety factor].

Inhalation

An acute inhalation PoD was selected from a recently submitted special acute inhalation study (2010, MRID 48139303) based on lung and plasma ChE inhibition (LOAEL = 3.7 mg/m^3; NOAEL not established). In this special acute inhalation study, adult female rats (Crl:CD(SD)) were exposed nose only to atmospheric concentrations of 0, 3.7, 12.9, 22.1 or 53.5 mg/m^3 for six hours and allowed an additional 72 hours to recover. Using the Agency's Reference concentration (RfC) methodology, a human equivalent concentration (HEC) was calculated and used to assess acute bystander exposure and risks. The HEC for acute bystander exposure is 0.62 mg/m^3.

Short- and intermediate-term inhalation risk assessments were based on two subchronic inhalation toxicity studies (MRID Nos.40013901, 40166501, 40908401) in the rat. Using the Agency's Reference concentration (RfC) methodology, a human equivalent concentration (HEC) was calculated and used to assess both occupational and residential exposure/risks. The short- and intermediate-term inhalation HEC calculated for residential exposures was converted to a NOAEL of 0.56 mg/kg/day to allow for comparison to estimated occupational inhalation doses (which are in units mg/kg). The HECs are based on no effects on plasma or RBC ChE inhibition identified from the two rat inhalation studies. For residential bystander exposure, the HEC for acute residential bystander exposure is 0.62 mg/m^{3,} and is 0.0057 mg/m^3 for short- and intermediate-term exposure. Because the 90-day study was conducted 5 days per week at 6 hours/day, the short- and intermediate-term residential HEC was adjusted to represent continual (24 hr, 7 day/week) exposure. In contrast, the occupational inhalation exposure was only adjusted to account for an 8 hour workday because worker exposure is expected to occur during the course of an average workweek (8 hours/day and 5 days/week).

For acute inhalation exposures, a total uncertainty factor of 300X was applied [3X for interspecies extrapolation (reduced from 10X because RfC methodology used which takes into consideration the pharmacokinetic differences between animals and humans), 10X for intraspecies variation, and a 10X FQPA database uncertainty factor (for extrapolation from a LOAEL to a NOAEL).

For short-term and intermediate- term inhalation exposures, a total uncertainty factor of 30X was applied [3X for interspecies extrapolation (reduced from 10X because RfC methodology used), 10X for intraspecies variation and a 1X FQPA SF (because the inhalation NOAEL is considered protective of pregnant females based on effects seen in the DNT at 0.3 mg/kg/day)].

Determination of Acute and Chronic Dietary PoDs for Chlorpyrifos Oxon

There is some potential for direct exposure to the oxon metabolite of chlorpyrifos, particularly from drinking water. BMD modeling of available oxon data for acute and repeated dosing studies was conducted (Appendix E, Tables 7 and 8). The purpose of this analysis is to

determine the toxicological PoDs for the oxon (Table 9) and to assess the relative potency of chlorpyrifos and its oxon metabolite.

A $BMDL_{10}$ of 0.05 mg/kg/day associated with RBC ChE inhibition in male rat pups exposed to chlorpyrifos oxon (acute dosing CCA study using oxon) was selected for the acute dietary PoD for the oxon. An uncertainty factor of 100X (10X to account for interspecies extrapolation and 10X for intraspecies variation) is applied to the $BMDL_{10}$ to obtain an aRfD of 0.0005 mg/kg/day. Based on the FQPA safety factor of 1, the acute population adjusted dose (aPAD) is 0.0005 mg/kg/day.

The chronic dietary PoD for chlorpyrifos oxon is selected from a $BMDL_{10}$ of 0.011 mg/kg/day from an 11 day repeat dosing CCA study using oxon and is based on inhibition of RBC ChE in adult female rats. A comparison of the resulting BMD_{10}s for juvenile and for adult rats indicates that juvenile rats are no more sensitive to the oxon than are adult rats. The BMDL10 for adult rats (0.011 mg/kg/day) was selected for the PoD because it was lower than that of the juvenile rats (0.025 mg/kg/day) and would be considered protective for juveniles. Uncertainty factors of 10X to account for interspecies extrapolation and 10X for intraspecies variation is applied to the $BMDL_{10}$ to obtain an aRfD of 0.00011 mg/kg/day. Based on the FQPA safety factor of 1, the chronic population adjusted dose (cPAD) is 0.000011 mg/kg/day.

Toxicity Factor for Chlorpyrifos Oxon. The Agency developed toxicity factors to estimate the potency of chlorpyrifos oxon relative to chlorpyrifos for the aggregate assessment. While the Agency uses the BMDL, not the BMD, for use as the PoD since the BMDL accounts for variability of the data, the BMD_{10} provides a point of comparison across studies and the BMD_{10} provides the basis for determining the relative toxicity of the chlorpyrifos oxon compared to chlorpyrifos. A toxicity factor for the oxon was calculated by dividing the chlorpyrifos BMD_{10} for the endpoint associated with the most sensitive compartment from the most sensitive sex for the duration of interest by the corresponding BMD_{10} for the oxon. Table 10 summarizes the toxicity values for chlorpyrifos oxon. Acute (all populations) toxicity factors of 8.8 (males) and 11.9 (females) were calculated from BMD analysis of inhibition of male and female pup RBC ChE (acute phase of the CCA study). The chronic toxicity factor of 18.0 was derived from BMD analysis of inhibition of RBC ChE in adult female rats (adult male rats not examined) observed in the repeated phase of the CCA study. The toxicity factors may be used in aggregate assessments where exposures to chlorpyrifos and the oxon are to be combined. Adjusting for relative toxicity will allow comparison of the combined exposures to a single PoD (since PoDs are different for chlorpyrifos and oxon).

4.8 Summary of Points of Departure and Toxicity Endpoints Used in Human Risk Assessment

Table 8 Summary of Toxicological Doses and Endpoints and Points of Departure for Chlorpyrifos for Use in Preliminary Dietary, Non-Occupational (Residential), and Occupational Human Health Risk Assessments

Exposure Scenario	Point of Departure (mg/kg/day)	Study and Toxicological Effects
Acute Dietary (all populations)	$BMDL_{10}$ = 0.36 UF_A = 10x UF_H = 10x FQPA SF = 1x Acute PAD = 0.0036	Inhibition of RBC ChE in male and female rat pups. Weight of evidence from several acute oral studies: • CCA Study (MRID 48139301) in the rat – PND 11 male and female • Data on PND17 males , Moser *et al*.(2006) • Qualitative support from Timchalk *et al*. (2006) and Zheng *et al*. (2000) studies
Chronic Dietary (all populations)	$BMDL_{10}$ = 0.03 UF_A = 10x UF_H = 10x FQPA SF = 1x Chronic PAD = 0.0003	Inhibition of RBC ChE in rat dams (GD 6 – 20). Weight of evidence from studies including: • Developmental neurotoxicity study in pregnant (GD 6 - 20) rats (MRID 44556901) • Gavage study in pregnant (GD 6 – LD10) rats (MRID 44648101)
Short-Term Incidental Oral (1 – 30 days)	$BMDL_{10}$ = 0.1 UF_A = 10x UF_H = 10x FQPA SF = 1x Residential LOC for MOE=100	Inhibition of RBC ChE in PND 11 male rats. • 11 day repeat oral CCA study in the rat (MRID 48139301).
Intermediate – term Incidental Oral	$BMDL_{10}$ = 0.03 UF_A = 10x UF_H = 10x FQPA SF = 1x Residential LOC for MOE=100	See Chronic Dietary.
Dermal Short- (1 – 30 days) and Intermediate-Term (1-6 months)	NOAEL = 5 mg/kg/day [Absorbed dermal NOAEL = 0.15 (for use in comparative assessment using biomonitoring data)]	Plasma and RBC ChE inhibition. 21-day dermal study (NOAEL) and 4 day probe study (LOAEL) in adult rats (MRID 40972801).

Exposure Scenario	Point of Departure (mg/kg/day)	Study and Toxicological Effects
	UF_A = 10x UF_H = 10x FQPA SF = 1x (residential) Residential LOC for MOE=100 Occupational LOC for MOE =100	
Acute Inhalation	Inhalation LOAEL = 3.7 mg/m3 HEC = 0.62 mg/m3 (residential) UF_A = 3x UF_H = 10x FQPA UF_{DB} = 10x (LOAEL to NOAEL extrapolation (residential) Residential LOC for MOE=300	Lung ChE inhibition. • Special 6 hour acute inhalation study (MRID 48139303). (Aerosol)
Inhalation Short- (1 – 30 days) and Intermediate- (1 – 6 months)	NOAEL (calc from HEC) = 0.56 mg/kg/day (8-hr occupational) NOAELHEC = 0.0057 mg/m3 (24 hr residential) UF_A = 3x UF_H = 10x FQPA SF = 1x (residential) Residential LOC for MOE=30 Occupational LOC for MOE =30	Lack of effects in 2 rat inhalation studies at the highest dose tested: LOAEL is based on 43% plasma and 41% RBC ChE inhibition following oral doses of 0.3 mg/kg/day in the DNT study • Two 90-day inhalation studies and the rat DNT study (MRIDs 40908401; 40013901/ 40166501). (Vapor study)

Point of Departure (PoD) = A data point or an estimated point that is derived from observed dose-response data and used to mark the beginning of extrapolation to determine risk associated with lower environmentally relevant human exposures. NOAEL = no observed adverse effect level. LOAEL = lowest observed adverse effect level. UF = uncertainty factor. UF_A = extrapolation from animal to human (interspecies). UF_H = potential variation in sensitivity among members of the human population (intraspecies). UF_L = use of a LOAEL to extrapolate a NOAEL. UF_{DB} = to account for the absence of key data (i.e., lack of a critical study) or other residual uncertainties as evidenced by available data. FQPA SF = FQPA Safety Factor. PAD = population adjusted dose (a = acute, c = chronic). RfD = reference dose. RfC = reference concentration. HEC = human equivalent concentration. MOE = margin of exposure. LOC = level of concern. N/A = not applicable.

Table 9 Summary of Points of Departure, Toxicological Doses and Toxicity Endpoints for Chlorpyrifos oxon for Use in Dietary Exposure Risk Assessments

Exposure/ Scenario	Point of Departure	Uncertainty/FQPA Safety Factors	RfD, PAD, Level of Concern	Study and Toxicological Effects
Acute Dietary (General Population, including Infants and Children)	$BMDL_{10}$ = 0.05	UF_A= 10x UF_H=10x FQPA SF = 1x	Acute RfD = 0.0005 aPAD =0.0005 mg/kg/day	CCA Study (oxon), acute dosing – Inhibition of RBC ChE in male rat pups
Chronic Dietary (All Populations)	$BMDL_{10}$ = 0.011	UF_A= 10x UF_H=10x FQPA SF= 1x	Chronic RfD = 0.00011 mg/kg/day cPAD = 0.00011 mg/kg/day	CCA Study (oxon), 11 day repeat dosing – Inhibition of RBC ChE in adult female rats

Point of Departure (PoD) = A data point or an estimated point that is derived from observed dose-response data and used to mark the beginning of extrapolation to determine risk associated with lower environmentally relevant human exposures. NOAEL = no observed adverse effect level. LOAEL = lowest observed adverse effect level. UF = uncertainty factor. UF_A = extrapolation from animal to human (interspecies). UF_H = potential variation in sensitivity among members of the human population (intraspecies). UF_L = use of a LOAEL to extrapolate a NOAEL. UF_{DB} = to account for the absence of key data (i.e., lack of a critical study) or other residual uncertainties as evidenced by available data. FQPA SF = FQPA Safety Factor. PAD = population adjusted dose (a = acute, c = chronic). RfD = reference dose. RfC = reference concentration. MOE = margin of exposure. LOC = level of concern. N/A = not applicable.

Table 10 Acute and Chronic Relative Toxicity Factors for Chlorpyrifos Oxon (Compared to Chlorpyrifos)

Dietary Scenario	Toxicity Factor (based on BMD_{10} comparison)
Acute Dietary (all populations)	12 ♀ (8.8♂)
Chronic Dietary (all populations)	18

4.9 Endocrine Disruption

As required by FIFRA and FFDCA, EPA reviews numerous studies to assess potential adverse outcomes from exposure to chemicals. Collectively, these studies include acute, subchronic and chronic toxicity, including assessments of carcinogenicity, neurotoxicity, developmental,

reproductive, and general or systemic toxicity. These studies include endpoints which may be susceptible to endocrine influence, including effects on endocrine target organ histopathology, organ weights, estrus cyclicity, sexual maturation, fertility, pregnancy rates, reproductive loss, and sex ratios in offspring. For ecological hazard assessments, EPA evaluates acute tests and chronic studies that assess growth, developmental and reproductive effects in different taxonomic groups. As part of its reregistration decision, EPA reviewed these data and selected the most sensitive endpoints for relevant risk assessment scenarios from the existing hazard database. However, as required by FFDCA section 408(p), chlorpyrifos is subject to the endocrine screening part of the Endocrine Disruptor Screening Program (EDSP).
EPA has developed the EDSP to determine whether certain substances (including pesticide active and other ingredients) may have an effect in humans or wildlife similar to an effect produced by a "naturally occurring estrogen, or other such endocrine effects as the Administrator may designate." The EDSP employs a two-tiered approach to making the statutorily required determinations. Tier 1 consists of a battery of 11 screening assays to identify the potential of a chemical substance to interact with the estrogen, androgen, or thyroid (E, A, or T) hormonal systems. Chemicals that go through Tier 1 screening and are found to have the potential to interact with E, A, or T hormonal systems will proceed to the next stage of the EDSP where EPA will determine which, if any, of the Tier 2 tests are necessary based on the available data. Tier 2 testing is designed to identify any adverse endocrine-related effects caused by the substance, and establish a dose-response relationship between the dose and the E, A, or T effect.

Under FFDCA section 408(p), the Agency must screen all pesticide chemicals. Between October 2009 and February 2010, EPA issued test orders/data call-ins for the first group of 67 chemicals, which contains 58 pesticide active ingredients and 9 inert ingredients. Chlorpyrifos was included on that list and has been issued an order to conduct the Tier 1 testing. For further information on the status of the EDSP, the policies and procedures, the list of 67 chemicals, future lists, the test guidelines and the Tier 1 screening battery, please visit our website: http://www.epa.gov/endo/.

5.0 Dietary Exposure and Risk Assessment

5.1. Residues of Concern Summary and Rationale

Plants - The qualitative nature of the residue in plants is adequately understood based on acceptable metabolism studies. The terminal residue of concern in/on plants is chlorpyrifos.

Livestock - The qualitative nature of residue in animals is adequately understood based on acceptable poultry and ruminant metabolism studies. The residue of concern in animals is chlorpyrifos.

Drinking water- The cholinesterase inhibiting metabolite, chlorpyrifos oxon, which has been characterized as having higher toxicity than chlorpyrifos, has been detected in environmental samples including drinking water, surface water, precipitation, and air. The residues of concern for drinking water are chlorpyrifos and the chlorpyrifos oxon.

Table 11 Summary of Metabolites and Degradates to be included in the Risk Assessment and Tolerance Expression

Matrix		Residues included in Risk Assessment	Residues included in Tolerance Expression
Plants	Primary Crop	Chlorpyrifos parent only	Chlorpyrifos parent only
	Rotational Crop	NA	NA
Livestock	Ruminant	Chlorpyrifos parent only	Chlorpyrifos parent only
	Poultry	Chlorpyrifos parent only	Chlorpyrifos parent only
Drinking Water		Chlorpyrifos and Chlorpyrifos oxon	NA

NA = Not Applicable

The chlorpyrifos degradate TCP is not considered a residue of concern as it does not inhibit cholinesterase (separate human health risk assessments have been performed for TCP, which has its own toxicity database).

5.2 Food Residue Profile

Currently, no petitions for the establishment of new tolerances for chlorpyrifos are pending. The previously submitted petitions 7F7248 (alfalfa, alfalfa mixed stands, grass grown for hay or pasture), 3F4188 (barley grain and forage), and 3H5662 (barley, milling fractions) were withdrawn 05/07/2009.

New crop field trial studies have been submitted for cotton gin byproducts (MRID 46651202), tart cherries (MRID 46651201), aspirated grain fractions for soybean, sorghum and wheat (MRID 46640901), and grass forage and hay as part of a data call in related to the 2002 chlorpyrifos IRED. These studies were reviewed previously and regulatory conclusions are included here for all the commodities with the exception of grass forage and hay (original petition withdrawn). In addition, petitions for a PHI reduction for sweet potato and the registration of a microencapsulated formulation were submitted but the requests were cancelled and denied, respectively.

Studies submitted to support the registration of a microencapsulated formulation of chlorpyrifos showed over tolerance residues after a foliar application of Lorsban 4E end use product to lemon with a rate of 6 lb ai/A. The maximum residue observed was 1.41 ppm while the tolerance for citrus fruit (CG 10) is 1.0 ppm. The label of the existing Lorsban 4E end use product (44.9% chlorpyrifos) allows a maximum application rate of 6.4 lb ai/A and addition of oil to the spray mixture. Under these conditions residues over tolerance may occur; therefore, HED recommends a reassessment of the tolerance for citrus fruit using lemon as the representative commodity.

The crop field trial data requested in the IRED and submitted by the petitioner is considered adequate to conclude that tolerances of 15 ppm and 22 ppm would cover any residues of

chlorpyrifos on cotton gin by products and aspirated grain fractions, respectively, and would support the current tolerance level for tart cherries under the condition that only dormant/delayed dormant and trunk spray applications are allowed on the label of the 75% WDG end use product. Acceptable storage stability data (in cherry, alfalfa forage, alfalfa hay and corn grain matrices) is available to support the storage conditions and durations of the samples of tart cherries, cotton and aspirated grain fractions used in these studies.

The dietary burden to livestock was recalculated to consider residues at tolerance level in the feedstock commodities (aspirated grain fractions and cotton gin byproducts) and to use the most current version of Table 1 of the OPPTS Test Guidelines 860.1000, released on June 2008. Based on the residues observed in the feeding study of cattle beef, dairy cow, swine and poultry at the 1x level or higher, HED concludes that the possible residues observed on livestock commodities (from animals fed with feedstock that may contain residues resulting from legal applications) are covered by the current tolerances established in the 40 CFR §180.342.

According to the revised version of Table 1of the OPPTS 860.1000, several studies are required to establish a tolerance for feed items and/or processed commodities that correspond to RACs treated with chlorpyrifos. Tolerances are required for residues of chlorpyrifos on wheat, milled byproducts; wheat, hay; corn, milled byproducts; cotton, meal, hulls and refined oil; and soybean, meal, hulls and refined oil. A magnitude of the residue study to establish a tolerance for wheat hay was required in the previous RED and has not been received. A tolerance was previously established for wheat milling fractions excluding flour as 1.5 ppm. Also, for corn milled byproducts a tolerance of 0.1 ppm was previously recommended based on concentration factors from 1.25x in grits to 2x in flour (D188151, S. Knizner, 20/Aug/1993). Tolerances for residues of chlorpyrifos on wheat milled byproducts and corn milled byproducts should be included in the 40 CFR §180.342. For cotton, processing studies are required to establish tolerances in cotton meal, cotton hulls and refined oil. Similarly, for soybean, processing studies are required to establish tolerances in soybean meal, hulls and refined oil.

[For details of the residue chemistry evaluations see I. Negrón-Encarnación, 5/24/11, D388164, *Chlorpyrifos. Registration Review Action for Chlorpyrifos. Summary of Analytical Chemistry and Residue Data*].

5.3 Water Residue Profile

EFED provided a drinking water assessment (DWA) which includes estimated drinking water concentrations (EDWCs) based on Tier II surface water and Tier I groundwater model simulations for currently registered uses of chlorpyrifos based on the most recent label data report provided by BEAD (R. Bohaty, 06/30/11, D368388 and D389480, *Revised Preliminary Registration Review Chlorpyrifos Drinking Water Assessment*). Tier II surface water EDWCs are more conservative than the Tier I groundwater EDWCs; therefore, only surface water EDWCs are discussed in the section below. This preliminary DWA also considers several sources of monitoring data including datasets from state as well as national programs. Below is a very brief summary of the DWA; see D368388/D389480 for a comprehensive characterization of the drinking water assessment.

EDWCs are provided for chlorpyrifos and chlorpyrifos oxon, a known transformation product of chlorpyrifos. EDWCs for chlorpyrifos oxon were derived from EDWCs calculated for chlorpyrifos because there are limited environmental fate data available for chlorpyrifos oxon and chlorpyrifos is expected to transform to chlorpyrifos oxon during drinking water treatment. Chlorpyrifos EDWCs were multiplied by 0.9541 (molecular weight correction factor) and 100% (maximum conversion during water purification) to generate chlorpyrifos oxon EDWCs. A 100% conversion factor for the oxidation of chlorpyrifos to chlorpyrifos oxon was used as an approximation based on bench scale laboratory data that indicate chlorpyrifos rapidly oxidizes to form chlorpyrifos-oxon almost quantitatively during typical water treatment.[8] Currently, there are no data available on the removal efficiency of chlorpyrifos prior to oxidation to chlorpyrifos oxon, or the removal efficiency of chlorpyrifos oxon. Stability studies indicate that once chlorpyrifos oxon forms during treatment little transformation is likely to occur before consumption (drinking water distribution).[5,9,10] It is possible that some drinking water treatment procedures such as granular activated carbon filtration and water softening (increased rate of chlorpyrifos-oxon hydrolysis at pH > 9) may reduce the amount of chlorpyrifos oxon in drinking water. It is unlikely that these treatment processes significantly reduce the amount of chlorpyrifos-oxon in drinking water. In addition, these treatment methods are not typical practices across the country for surface water. For these reasons, chlorpyrifos-oxon is the residue of concern for drinking water. Additional discussion of the effects of drinking water treatment on chlorpyrifos and chlorpyrifos oxon are provided in the EFED Drinking Water Assessment. Another degradation product of chlorpyrifos, 3,5,6-trichloro-2-pyridinol (TCP) is not examined in this assessment as it is no longer considered to be of toxicological concern.

Tier II modeled (surface water) chlorpyrifos-oxon EDWCs for grapes, corn/soybean and sugar beets are provided in Table 12. These water scenarios are based on both the average typical and maximum label use rates unless otherwise noted in the drinking water assessment. Grape, corn/soybean and sugar beet were singled out for this preliminary drinking water assessment as representative crops because there is a large amount (>100,000 lb) of chlorpyrifos applied to these crops per year, a substantial portion (percent crop treated/percent crop planted) of these crops are treated with chlorpyrifos, and/or the use locations are distributed throughout the United States. In addition, the reported EDWCs for grapes, corn/soybean and sugar beets are generally representative of the other chlorpyrifos use scenarios modeled when EDWCs are compared. All EDWCs for all modeled chlorpyrifos use scenarios are provided in EFED's DWA. Because chlorpyrifos is registered for use on turf (including sod farms, golf courses, road medians, and industrial areas) a percent cropped area (PCA) of 1 (considers 100% of the watershed is treated) was applied to modeling results a standard procedure in EFED. If chlorpyrifos were not used on turf, a PCA value of 0.87 (87% of the watershed is treated) would have been used based on the other crops chlorpyrifos is currently registered for use on; therefore, the EDWCs would be reduced by 13% if turf were not a registered use. This reduction is not expected to alter the conclusions of this risk assessment.

[8] Duirk, S. E.; Collette, T. W.; Degradation of Chlorpyrifos in Aqueous Chlorine Solutions: Pathways, Kinetics, and Modeling. *Environ. Sci. Technol.*, 2006, *40(2)*, 546-550.
[9] Wu, J.; Laird, D. A. Abiotic Transformation of Chlorpyrifos to Chlorpyrifos Oxon in Chlorinated Water. *Environ. Toxcol.Chem.*, **2003**, 22(2), 261-264.
[10] Tierney, D. P.; Christensen, B. R.; Culpepper, V. C. Chlorine Degradation of Six Organophosphate Insecticides and Four Oxons in Drinking Water Matrix. *Submitted by Syngenta Crop Protection, Inc.* **2001**.

Table 12 Estimated Drinking Water Concentrations of Chlorpyrifos-oxon Resulting From Chlorpyrifos Use on Grapes, Corn/Soybean and Sugar beets

Crop Scenario	Chlorpyrifos Oxon (ppb) Average Typical Rate			Chlorpyrifos Oxon (ppb) Maximum Rate		
	1-in-10 Year Peak	1-in-10 Year Annual Average	30 Year Annual Average	1-in-10 Year Peak	1-in-10 Year Annual Average	30 Year Annual Average
Grapes L.R.	2.76	0.41	0.25	107.05	14.06	9.38
Corn/soybean (a)	4.19	0.78	0.48	29.49	4.39	2.98
Sugar Beets	14.36	4.3	1.85	10.06	1.07	0.65

LR= lower rate of two grape application scenarios.

(a) Soybean was only evaluated at the maximum label rate for drinking water.

BEAD provided typical use information to EFED to help refine its assessment. In general, preliminary analysis suggest that typical single application rates correlate well with the modeled single application rates; however, in general the number of applications typically applied each year is less than the maximum allowed on the label. The results of this analysis can also be found in EFED's DWA but are not currently consider in this assessment. Typical agronomic practices also vary from those modeled. In general, the farming methods used over the last five years result in EDWCs that are lower than the most vulnerable scenarios allowed on current labels. Submission of typical use rates and agronomic practices will assist EFED in further refine its final DWA for chlorpyrifos.

There are two modeled chlorpyrifos use scenarios that result in EDWCs that are substantially higher than the majority of the modeled chlorpyrifos use scenarios. These use scenarios are for grape (high rate; 33 lb ai/A) and turf. The EDWCs reported for Grape HR (high rate; 33 lbs a.i./acre) are the result of a high application rate trunk drench/soil application which is currently permitted on labels and may not represent actual or intended use of chlorpyrifos on grape. Some recently approved labels restrict the use of chlorpyrifos on grape to 6 lbs a.i./a. The EDWCs reported for Turf FA (frequent applications) is based on 26 applications (limit of PRZM-EXAMS) and a 3 day application interval. This scenario was developed to highlight the uncertainty associated with the unrestricted use of chlorpyrifos on turf (turf labels do not currently restrict the number of chlorpyrifos applications per year or the maximum number of applications of chlorpyrifos per year) and may not may not represent actual or intended use of chlorpyrifos on turf. Because of the uncertainties with these labels, these modeled EDWCs were not used in the preliminary dietary (water) risk assessment for chlorpyrifos.

Water monitoring data from the USGS National Water-Quality Assessment Program (NAWQA), USEPA/USGS Pilot Reservoir Monitoring Program, USDA Pesticide Data Program (PDP), California Department of Pesticide Regulation (CDPR), and National Center for Water Quality Research (NCWQR) at Heidelberg College were evaluated in reference to an acute exposure to chlorpyrifos and its degradation product chlorpyrifos oxon. The monitoring data show chlorpyrifos detections at low concentrations, generally not exceeding 0.5 µg/L. For example, USGS NAWQA, which contains an extensive monitoring dataset for chlorpyrifos and chlorpyrifos oxon, reports a peak chlorpyrifos detection of 0.57 µg/L in surface water with a detection frequency of approximately 15%. CDPR and NCWQR have detected chlorpyrifos

concentrations greater than 1 ppb in surface water on several occasions. Peak concentrations of chlorpyrifos observed for CDPA and NCWQR are 3.96 and 24 ug/L, respectively. Note the data from NCWQR have not been thoroughly reviewed at this time, but are supplemental. In addition, the NCWQR data are pre-RED and subsequent mitigation. Therefore, it is unclear if NCWQR monitoring data represent current chlorpyrifos uses. EFED is in the process of acquiring more recent data from NCWQR and conducting a more thorough review of the NCWQR data.

In general, the monitoring data include sampling sites that represent a wide range of aquatic environments including small and large water bodies, rivers reservoirs, and urban and agricultural locations. The sampling sites also vary by year and there are limited sampling data available for some areas in the United States where chlorpyrifos is used. None of the monitoring programs were specifically designed to target chlorpyrifos use; therefore, peak concentrations of chlorpyrifos and chlorpyrifos oxon likely went undetected in these programs. Sampling frequencies in high chlorpyrifos use areas are not be designed to capture peak concentrations. The sample frequencies vary from bimonthly to only once per year depending on the program and the sampling site with the exceptions of NCWQR. NCWQR sample frequencies range from daily to monthly. For atrazine (90 day exposure concern) CWS monitoring sampling frequency of 7 days was chosen to be appropriate; however, a recent SAP agreed that a duration of exposure concern that is less than 7 days, such is the case for chlorpyrifos or chlorpyrifos oxon, would likely require even more frequent sampling to capture peaks. This is supported by the NCWQR data as well as PRZM-EXAMS model output time series data and underscores the need for frequent sampling in order to detect peak chlorpyrifos concentrations.

In summary, the monitoring programs analyzed in EFED's DWA do not specifically target chlorpyrifos; consequently, detections cannot be directly associated with a particular use pattern or site nor are the detections expected to represent the potential peak exposure to chlorpyrifos or chlorpyrifos oxon. Additional discussion of the monitoring data can be found in the DWA and is not further discussed in this assessment as it is not considered an appropriate estimation of the potential exposure to chlorpyrifos and chlorpyrifos oxon. The monitoring data were only analyzed in reference to an acute exposure estimation and additional analysis is needed in order to determine if the data contained in the various datasets can be used for longer term exposure durations (i.e., chronic).

DWA Uncertainties

EFED has noted several uncertainties associated with the use of chlorpyrifos. The uncertainties and assumptions are highlighted below.

- While the predominate water treatment method used to disinfect drinking water throughout the United States is chlorination, there are other treatment methods that may reduce chlorpyrifos or chlorpyrifos-oxon exposure concentrations. For facilities that utilize alternative methods, the laboratory data showing 100% conversion of chlorpyrifos to chlorpyrifos-oxon during water purification may not be applicable. Therefore, the chlorpyrifos oxon exposure values presented here may be overestimated for those facilities. Additionally, the oxon may be partially removed with certain treatment processes. In order to reduce the uncertainty associated with the EDWCs reported in this

DWA, additional data including both targeted monitoring data as well as data on the removal efficiency of chlorpyrifos and chlorpyrifos-oxon during treatment is needed. This assessment does not take into account the potential loss of mass (either chlorpyrifos or chlorpyrifos-oxon) during treatment from methods such as activated carbon, sedimentation, water softening, etc., as these treatment methods as well as the sequence of these treatment methods vary considerably across the country. Therefore, for systems that do utilize such treatment methods, the EDWCs reported in this assessment may be higher than the likely exposure concentrations in drinking water. The amount of overestimation is unknown, as currently there are no data available on the removal efficiency of either chlorpyrifos or chlorpyrifos-oxon by these various treatment methods and sequences of treatments. The exception is for water softening where laboratory data can be used to calculate the rate of hydrolysis under water softening conditions ($pH \geq 11$) for both chlorpyrifos and chlorpyrifos-oxon. Water softening, however, is not a common treatment process for surface water.

- Chlorpyrifos is registered for use on turf (including sod farms, golf courses, road medians, and industrial areas), therefore, a percent cropped area (PCA) of 1 (100% of the watershed is treated) was applied to the modeling results in order to cover the use on non-agricultural land. If chlorpyrifos was not registered on turf, the default PCA value of 0.87 (87% of the watershed is treated) would have been used. EFED is currently working on developing crop specific PCAs. For the final DWA, a turf specific PCA may be available to help further refine this assessment. This assessment is national in scope covering multiple chlorpyrifos uses; therefore, it does not take into account regional PCA values (e.g., 0.87 for Missouri, 0.82 for Ohio, 0.07 for Upper Colorado, etc.) or PCA values that represent only a single or a few crops (e.g., 0.46 for corn, 0.83 for corn and soybean, etc.).

- The monitoring programs analyzed for this drinking water assessment do not specifically target chlorpyrifos. Consequently, detections cannot be directly associated with a particular use pattern or site, nor are the detections expected to represent the potential peak chlorpyrifos or chlorpyrifos-oxon exposures. In order to reduce uncertainties and help refine the current exposure assessment, EFED is seeking to incorporate targeted monitoring data in its drinking water assessment.

- Meteorological data and crop profiles, as well as best professional judgment, were used to establish an application date for modeling; however, the selected date may not represent the intended or actual application dates. The application date used for model runs can significantly alter the EDWCs; thus, EDWCs reported could over or under predict the potential exposure. For some chlorpyrifos use scenarios several application dates were evaluated. In general, the date that provided the most conservative EDWCs and corresponded to the appropriate pest pressure are reported. A brief examination of the variation in peak EDWCs for some of the multi-run scenarios ranged from 3-23% for peak EDWCs. Scenarios examined included those that resulted in high and low EDWCs. Based on this limited examination, the application date chosen for modeling can change the peak EDWCs by as much as 23%. This is only an estimate and may vary depending

on the scenario (soil and metrological data) and may not represent all chlorpyrifos use scenarios.

- Many chlorpyrifos labels include application restrictions on a per season basis; however, for some crops there can be multiple seasons per year. For modeling purposes one season was considered to be equal to one year unless otherwise noted. If multiple crop seasons are possible per year it is conceivable that the EDWCs reported in this document may underestimate the actual exposure. In general, this assessment makes conservative assumptions regarding re-cropping and rotations. EFED evaluated a number of labels for specific information regarding application methods and timing, and noted some application rates provided on the label are on a per season basis. The yearly application rates used in this assessment are primarily based on data from BEAD's label data report. The typical use data provided by BEAD to date do not inform this uncertainty as the typical use rate information was not provided for crops that may have multiple seasons per year.

- Some of the labels do not provide maximum single or annual application rates for chlorpyrifos or application retreatment intervals. When this information is not specified on the label, a conservative application scenario was developed and modeled. For example, several labels permit trunk sprays (e.g., some orchard fruit and nut trees such as apples and almonds), at a dilution rate in lbs a.i./100 gallons of water; however, the amount of the dilution that can be applied is not stated on the label. The application rate was assumed to be lb a.i./a. It is unclear if this approach is representative of the intended or actual use scenarios. However, we did find that the average typical application rate provided by BEAD for apples was consistent with the assumed application rate for apples (trunk drench) made for modeling purposes. The extent to which actual use rates may be different is uncertain.

- Some labels restrict the amount of a specific chlorpyrifos formulation; however, the total amount of chlorpyrifos that can be applied per year is not provided. Therefore, the use of multiple chlorpyrifos-containing products is possible. This assessment does not consider the combined use of multiple chlorpyrifos containing products that contain such language, but if such use occurs the reported EDWCs in this assessment may not account for this event.

- Application rates (maximum single applications and yearly/seasonal) vary between labels. Recently approved labels better define chlorpyrifos use; however, there are still several older active labels that do not provide application restrictions or have higher maximum single and/or yearly applications rates than recently approved labels. The most conservative scenarios (highest applications rates) were modeled unless otherwise noted. In order to reduce the uncertainty associated with the EDWCs reported in this preliminary DWA, all chlorpyrifos labels should be updated to clearly state maximum yearly and single application rates, as well as minimum retreatment intervals.

- The monitoring programs analyzed in EFED's DWA do not specifically target chlorpyrifos; consequently, detections cannot be directly associated with a particular use pattern or site nor are the detections expected to represent the potential peak exposure to chlorpyrifos or chlorpyrifos oxon. In order to reduce the uncertainty associated with the interpretation of monitoring data EFED is seeking to incorporate targeted monitoring data in its DWA. Submission of such data would help refine the final risk assessment.

5.4 Dietary Risk Assessment

5.4.1 Description of Residue Data Used in Dietary Assessment

Highly refined acute and chronic dietary (food only, food and drinking water, and drinking water only) exposure and risk assessments of chlorpyrifos were conducted using the Dietary Exposure Evaluation Model DEEM-FCID™, Version 2.03. Risk estimates were determined for the general U.S. population and various population subgroups: all infants (<1 year old), children 1-2, children 3-5, children 6-12, youth 13-19, females 13-49, adults 20-49, and adults 50+ years.

Food residue data for the dietary assessment are almost entirely based upon PDP data. For crops not tested by PDP translations have been made from similar tested crops. Occasionally, older PDP data have been used where it represented the best estimate of real residues. Field trial data or tolerances have been used for a very few crops where translations from PDP data were not possible. The same data sources were used for both the acute and chronic assessments. Most input residues for the acute assessments were incorporated as residue distributions. Input residues for the chronic assessments were applied as a single point estimate (for detailed assumptions, inputs and results see D. Soderberg, 6/30/11, D388166, *Chlorpyrifos Revised Acute (Probabilistic) and Chronic Dietary Exposure and Risk Assessments for Food Only (with and without Food Handling Use included) and for Water Only for the Registration Review Action: Typical Use Rates/Water Included.*

Processing factors from cooking and processing studies were employed where available.

From PDP (and BEAD) data it appears that chlorpyrifos is either applied to a variety of crops which lack the necessary tolerances for chlorpyrifos, or possibly that residues may have occurred on several crops that are rotated in after use of chlorpyrifos on a registered crop. Residues in catfish (no tolerance) were also reported by PDP. Data on agricultural commodities without tolerances are not ordinarily included in HED assessments and were not included in this assessment. Omission of residues on these commodities may lead to underestimation of exposure in the current assessment.

Environmental Fate and Effects Division (EFED) has provided chlorpyrifos and chlorpyrifos-oxon estimated drinking water concentrations (EDWCs) for chlorpyrifos use on grapes, corn/soybean and sugar beets in order to provide a range of possible EDWCs representing the many registered chlorpyrifos uses. In general, these grape, corn/soybean and sugar beet uses represent a broad range of higher end, middle, and lower end EDWCs, respectively, modeled for all chlorpyrifos uses. These particular uses were selected as representative crops for this

preliminary drinking water assessment because there is a large amount of chlorpyrifos applied to these crops per year, a large portion of these crops are treated with chlorpyrifos, and/or the use locations are distributed throughout the United States. All estimated drinking water concentrations used in this assessment are based upon the PRZM-EXAMS model (Table 12 above). For the chronic assessment the 1-in-10 year annual means from PRZM-EXAMS were used. For acute, a distribution of the modeled EDWCs was incorporated into the assessment.

The residues of concern for chlorpyrifos in food are for the parent chlorpyrifos only. Residues of concern in drinking water may include both parent and oxon. All drinking water residues were assumed to be in the form of the oxon as scientific literature suggests rapid and complete conversion of chlorpyrifos to chlorpyrifos-oxon during drinking water disinfection and also show that the oxon is relatively stable after drinking water disinfection. For the preliminary dietary assessment, residues in food are assumed to consist of parent chlorpyrifos only, while residues in water are assumed to consist of chlorpyrifos-oxon only. Therefore food exposures are assessed to toxicological points of departure (PoDs) based upon the toxicity of the parent and water exposures are assessed to PoDs based upon the toxicity of the oxon.

5.4.2 Percent Crop Treated Used in Dietary Assessment

BEAD provided percent crop treated information for over 50 crops [Chlorpyrifos (059101) Screening Level Usage Analysis (SLUA), dated 3/10/2010, and Addendum; see Attachment 3 of D388166]. Where supplied, maximum percent crop treated estimates were used in the acute dietary risk assessment and average percent crop treated estimates were used in the chronic dietary risk assessment. 100% crop treated values were assumed for the following: bananas, figs, radishes, rutabaga roots, turnip roots and greens, garlic, shallots, Brussels sprouts, kohlrabi, collards, kale, mustard and rapeseed greens, citron, citrus hybrids, limes, pommelos, and triticale. BEAD also estimated that less than 2% (default value) of food handling establishments are treated with chlorpyrifos.

5.4.3 Acute Dietary Risk Assessment

The most highly exposed population subgroup for food only was children 1-2, at 9.0% aPAD. The exposure for the general U.S. population from food was 5.1%. Residues in peaches, peppers, apples, plums grapefruit juice, grape juice, soy milk, cranberry juice and orange juice were generally drivers of acute food exposure. (Residues on fresh peaches, plums and peppers in particular strongly tend to be on the imported crops rather than on domestically grown crops.)

For water alone using the lower end representative water scenario (sugar beet) the acute exposure for the general U. S. population ranged from 61-99% of the aPAD based upon the chlorpyrifos-oxon PoD for the maximum and typical application rates, respectively. For all infants, the most highly exposed subpopulation, the exposure ranged from 210-340% of the aPAD for the maximum and typical application rates, respectively.

For water alone using the mid-range representative scenario (corn) the acute exposure for the general U. S. population ranged from 38-240% of the aPAD based upon the chlorpyrifos-oxon PoD for the typical and maximum application rates, respectively. For all infants, the most highly

exposed subpopulation, the exposure ranged from 120-770% aPAD for the typical and maximum application rates, respectively.

For water alone using the higher end representative scenario (grape) the acute exposure for the general U.S. population ranged from 19-810% of the aPAD based upon the chlorpyrifos oxon for the typical and maximum application rates, respectively. For all infants, the most highly exposed subpopulation, the exposure ranged from 59-2700% aPAD for the typical and maximum application rates, respectively.

Table 13 Summary of Preliminary Acute Dietary Food Only Exposure and Risk (Using Parent Chlorpyrifos PoD)

Population Subgroup	Acute Food Only(99.9th percentile) **[Chlorpyrifos aPAD= 0.0036 (includes 1x FQPA Factor)]**	
	Dietary Exposure (mg/kg/day)	% aPAD
General U.S. Population	0.000182	5.1
All Infants (< 1 year old)	0.000190	5.3
Children 1-2 years old	**0.000323**	**9.0**
Children 3-5 years old	0.000275	7.6
Children 6-12 years old	0.000196	5.4
Youth 13-19 years old	0.000122	3.4
Adults 20-49 years old	0.000161	4.5
Adults 50+ years old	0.000170	4.7
Females 13-49 years old	0.000150	4.2

Table 14 Summary of Preliminary Acute Drinking Water Only Exposure and Risk (at the 99.9th Percentile Exposure; Using the Chlorpyrifos-oxon PoD)

Population Subgroup	Lower End Representative Water Scenario (a) (Sugar Beet)		Mid-Range Representative Water Scenario (a) (Corn)		Higher End Representative Water Scenario (a) (Grape)	
	Exposure (µg/kg/day) (% aPAD)		Exposure (µg/kg/day) (% aPAD)		Exposure (µg/kg/day) (% aPAD)	
	Average Typical Rate	Maximum Rate	Average Typical Rate	Maximum Rate	Average Typical Rate	Maximum Rate
General U.S. Population	0.496 (99%)	0.304 (61%)	0.192 (38%)	1.192 (240%)	0.095 (19%)	4.090 (810%)
All Infants (< 1 year old)	**1.677 (340%)**	**1.029 (210%)**	**0.608 (120%)**	**3.840 (770%)**	**0.294 (59%)**	**13.415 (2700%)**
Children 1-2 years old	0.724 (140%)	0.445 (89%)	0.271 (54%)	1.689 (340%)	0.132 (26%)	5.856 (1200%)
Children 3-5 years old	0.654 (130%)	0.404 (81%)	0.242 (48%)	1.526 (310%)	0.118 (24%)	5.259 (1100%)
Children 6-12 years old	0.452 (90%)	0.281 (56%)	0.169 (34%)	1.055 (210%)	0.082 (16%)	3.683 (740%)
Youth 13-19 years old	0.384 (77%)	0.238 (48%)	0.147 (29%)	0.912 (180%)	0.072 (14%)	3.151 (630%)
Adults 20-49 years old	0.442 (88%)	0.270 (54%)	0.164 (33%)	1.026 (210%)	0.081 (16%)	3.538 (710%)
Adults 50+ years old	0.398 (80%)	0.248 (50%)	0.138 (28%)	0.882 (180%)	0.069 (14%)	3.059 (610%)
Females 13-49 years old	0.440 (88%)	0.269 (54%)	0.162 (32%)	1.020 (200%)	0.081 (16%)	3.533 (710%)

Chlorpyrifos-oxon aPAD (includes 1x FQPA Factor) = 0.0005 mg/kg/day or 0.5 µg/kg/day

(a) Lower-end, Mid-range and Higher-end representative scenarios determined based on maximum application rate.

5.4.4 Chronic Dietary Risk Assessment

The chronic dietary exposure assessment was performed with and without food handling establishment (FHE) uses. FHE exposures are more appropriately performed as a chronic dietary

assessment. An acute assessment is more likely to overestimate the risk for FHE exposures since there are no detectable residues in the FHE studies and the percent establishments treated were below the threshold where BEAD is able to accurately quantify.

The most highly exposed population subgroup for chronic food only (excluding FHE uses) were children 1-2, at 8.4 % cPAD, using a PoD based upon the toxicity of chlorpyrifos. The exposure for the general U.S. population from food without FHE use was 3.0 %cPAD. For food with FHE use included the exposure for the general U. S. population was 3.7% cPAD, and for the most highly exposed subpopulation, children 1-2, was 11% cPAD.

For water alone exposure to chlorpyrifos oxon, the risks span a large range, depending on the representative crop assessed (sugar beets, corn, grapes) and application rate. Using the lower end representative scenario (sugar beet) risk estimates did not exceed the level of concern based on the maximum application rates, however there were some risks of concern for average typical rates assessed for infants and children. The resulting risk estimates for the general U. S. population ranged from 21-82% cPAD using a PoD based upon the toxicity of chlorpyrifos-oxon for the maximum and typical rates, respectively. For the most highly exposed subpopulation, all infants, exposure ranged from 69-270 % cPAD depending on the application rate assessed. Drinking water risk estimates for the mid-range and high end representative scenarios (corn and grapes) were not of risk concern at the typical application rates (<49% cPAD) for the highest exposed population, infants (<1 yr), but exceeded the level of concern at the maximum application rates (ranged from 280-890% cPAD) for infants (<1 yr).

The results of the chronic dietary exposure analysis are reported in column 1 of Table 15 below. As can be seen, residues do not exceed the cPAD for any population subgroup. These food exposures are based only upon field use of chlorpyrifos and do not incorporate exposure from food handling establishment (FHE) uses. Estimated potential exposures from FHE uses were assessed separately from other food exposure as a matter of convenience and are provided in column 2 of Table 15, but are additive to the other food exposures. Therefore, column 3 of Table 15 shows the total chronic food plus FHE exposure. It should be noted that there is considerable uncertainty in the exposure estimates for FHE. There appear to be three currently registered FHE uses (labels), but BEAD has been unable to estimate a percent FHE treated and has defaulted to its minimum of 2%. In addition, the expected FHE residues are based upon an FHE residue study with no detectable residues (1/2 LOD is used for FHE anticipated residues).

Table 15 Summary of Preliminary Chronic Dietary Food Only Exposure and Risk (Using Parent Chlorpyrifos PoD)

Population Subgroup	**Chronic Food Only [Chlorpyrifos cPAD= 0.0003 (includes 1x FQPA Factor)]**		**Chronic Food Handling Establishment (FHE) Only [Chlorpyrifos cPAD= 0.0003 (includes 1x FQPA Factor)]**		**Chronic Food with FHE Only [Chlorpyrifos cPAD= 0.0003 (includes 1x FQPA Factor)]**	
	Dietary Exposure (mg/kg/day)	% cPAD	Dietary Exposure (mg/kg/day)	% cPAD	Dietary Exposure (mg/kg/day)	% cPAD
General U.S. Population	0.000009	3.0	0.000002	0.7	0.000011	3.7
All Infants (< 1 year old)	0.000012	4.0	0.000004	1.3	0.000016	5.3
Children 1-2 years old	**0.000025**	**8.4**	**0.000009**	**3.0**	**0.000034**	**11**
Children 3-5 years old	0.000021	7.1	0.000006	2.1	0.000027	9.2
Children 6-12 years old	0.000013	4.3	0.000004	1.3	0.000017	5.6
Youth 13-19 years old	0.000007	2.5	0.000002	0.6	0.000009	3.1
Adults 20-49 years old	0.000007	2.3	0.000001	0.5	0.000008	2.8
Adults 50+ years old	0.000007	2.4	0.000001	0.5	0.000008	2.9
Females 13-49 years old	0.000007	2.2	0.000001	0.5	0.000008	2.7

Table 16 Summary of Preliminary Chronic Drinking Water Only Exposure and Risk (Using the Chlorpyrifos-oxon PoD)

Population Subgroup	Lower End Representative Water Scenario (a) (Sugar Beet)		Mid-Range Representative Water Scenario (a) (Corn)		Higher End Representative Water Scenario (a) (Grape)	
	Exposure (µg/kg/day) (% cPAD)		Exposure (µg/kg/day) (% cPAD)		Exposure (µg/kg/day) (% cPAD)	
	Average Typical Rate	Maximum Rate	Average Typical Rate	Maximum Rate	Average Typical Rate	Maximum Rate
General U.S. Population	0.091 (82%)	0.023 (21%)	0.016 (15%)	0.093 (84%)	0.009 (7.9%)	0.297 (270%)
All Infants (< 1 year old)	**0.297 (270%)**	**0.076 (69%)**	**0.054 (49%)**	**0.304 (280%)**	**0.028 (26%)**	**0.974 (890%)**
Children 1-2 years old	0.135 (120%)	0.034 (31%)	0.024 (22%)	0.138 (130%)	0.013 (12%)	0.441 (400%)
Children 3-5 years old	0.126 (110%)	0.032 (29%)	0.023 (21%)	0.129 (120%)	0.012 (11%)	0.513 (380%)
Children 6-12 years old	0.087 (79%)	0.022 (20%)	0.016 (14%)	0.089 (80%)	0.008 (7.5%)	0.285 (260%)
Youth 13-19 years old	0.066 (60%)	0.017 (15%)	0.012 (11%)	0.067 (61%)	0.006 (5.7%)	0.215 (200%)
Adults 20-49 years old	0.085 (77%)	0.022 (20%)	0.015 (14%)	0.087 (79%)	0.008 (7.3%)	0.277 (250%)
Adults 50+ years old	0.089 (81%)	0.023 (21%)	0.016 (15%)	0.091 (83%)	0.008 (7.7%)	0.292 (270%)
Females 13-49 years old	0.084 (77%)	0.022 (20%)	0.015 (14%)	0.086 (78%)	0.008 (7.3%)	0.276 (250%)

Chlorpyrifos-oxon cPAD (includes 1x FQPA Factor) = 0.00011mg/kg/day or 0.11 µg/kg/day

(a) Lower-end, Mid-range and Higher-end representative scenarios determined based on maximum application rates.

5.4.5 Comparison of Dietary Results for Chlorpyrifos 2000 Risk Assessment and 2011 Preliminary Risk Assessment

For comparison purposes, Table 17 and Table 18 below present the acute and chronic PoDs and resulting dietary risk estimates (for the most highly exposed subpopulations only: young children and/or infants) for the June 2000 chlorpyrifos risk assessment and for the current 2011 preliminary assessment.

The acute and chronic PoDs and resulting dietary risk estimates (for the most highly exposed subpopulations only: young children and/or infants) are compared for the June 2000 chlorpyrifos risk assessment and for the current 2011 preliminary assessment.

In 2000 the acute and chronic dietary PoDs were based on NOAELs (plasma and/or RBC ChEI) from oral studies using adult laboratory animals (including pregnant females). The same PoD, based on toxicity of parent chlorpyrifos, was selected for both food and water. A 10x FQPA factor was retained.

For the 2011 preliminary assessment, the acute and chronic PoDs for *food* exposures were based on the toxicity of parent chlorpyrifos (BMDs for RBC ChEI) to juvenile and pregnant animals, respectively. The acute and chronic PoDs for *water* exposures were based on the toxicity of the chlorpyrifos oxon (BMDs for RBC ChEI) from studies where juvenile and adult animals were directly dosed with the oxon. A 1x FQPA factor is proposed.

The acute dietary (food only) risk estimates for the most highly exposed subpopulation were 82% of the aPAD (2000) and 9% of the aPAD (2011).

In 2000 the acute EDWC was not included in the dietary analysis (water residues not incorporated directly into DEEM analysis) and a % aPAD result was not calculated. Instead a Drinking Water Level of Concern (DWLOC) method was used. An estimated ≤18% aPAD value for 2000 water was estimated herein for comparison purposes only and reflects the exposure amount allowed for water in the 'risk cup' after food exposures are subtracted. In the 2011 preliminary water assessment, a range of representative scenarios was assessed (higher end, mid-range, and lower end). The resulting acute drinking water risk estimates (for infants) ranged from 59% to 340% aPAD for average typical application rates and from 210% to 2700% aPAD for the maximum application rates.

The chronic dietary (food only) risk estimates for the most highly exposed subpopulation were 51% of the cPAD (2000) and 11% of the cPAD (2011).

As in the 2000 acute water assessment, the 2000 chronic water assessment used a DWLOC approach. A ≤ 49% cPAD value was estimated for 2000 water. In the 2011 preliminary water assessment, a range of representative scenarios was assessed (higher end, mid-range, and lower end). The resulting chronic drinking water risk estimates (for infants) ranged from 26% to 270% cPAD for average typical application rates and from 69% to 890% cPAD for the maximum application rates.

It is important to note that, aside from differences in the PoDs and FQPA factors, there have been changes in the dietary input assumptions since 2000. For example, updated food monitoring data and percent crop treated data were used in the 2011 preliminary assessment. For water, in 2000 EDWCs were based on parent chlorpyrifos and were derived from the SCI-GROW model for groundwater and monitoring data for surface water. It is now believed that the existing water monitoring data are not representative of the potential exposure in drinking water and is not recommended for use in quantitative risk assessment. Groundwater EDWCs are expected to be low relative to surface water based on environmental fate characteristics of chlorpyrifos. Therefore, the SCI-GROW modeling results used in 2000 likely underestimate the potential exposure. The 2011 preliminary risk assessment has used a range of surface water EDWCs derived using PRZM-EXAMS modeling. In 2000 the residue of concern in drinking water was assumed to be parent chlorpyrifos. Empirical data indicate rapid conversion of chlorpyrifos to chlorpyrifos oxon during typical drinking water treatment; therefore, this preliminary assessment considers the oxon as the residue of concern in treated drinking water and assumes 100% conversion of chlorpyrifos to oxon. The chlorpyrifos oxon is more toxic than parent chlorpyrifos.

Table 17 Comparison of Chlorpyrifos Acute PoDs and Risk Estimates for 2000 Assessment and 2011 Preliminary Assessment

Acute Dietary Risks			
For highest exposed sub-population	**In 2000** Food and Water PoD (CPY): 0.5 mg/kg/day; total UF=1000 (FQPA=10x)	**In 2011** Food PoD (CPY): 0.36 mg/kg/day; total UF 100 (FQPA=1x) Water PoD (Oxon): 0.05 mg/kg/day; UF 100 (FQPA=1)	
	% aPAD	**% aPAD**	
		Average Typical Application Rate	Maximum Application Rate
Food	82	9.0 (a)	
Drinking Water			
Lower		340	210
Mid-range		120	770
Higher	Estimated ≤18*	59	2700
Aggregate	DWLOC method; not of concern	Not assessed in preliminary assessment	

* not calculated in 2000 (DWLOC method used); this estimated value represents the difference between the aPAD and food exposures, i.e. what was left in the risk cup for water after taking into account food exposures.

(a) Food estimates are highly refined and thus the average typical and maximum application rate scenarios are not applicable.

Table 18 Comparison of Chlorpyrifos Chronic PoDs and Risk Estimates for 2000 Assessment and 2011 Preliminary Assessment

Chronic Dietary Risks (includes FHE uses)			
For highest exposed sub-population	**In 2000** Food and Water PoD (CPY): 0.03 mg/kg/day; total UF=1000 (FQPA=10x)	**In 2011** Food PoD (CPY): 0.03 mg/kg/day; total UF 100 (FQPA=1x) Water PoD (Oxon): 0.011 mg/kg; UF 100 (FQPA=1x)	
	% cPAD	**% cPAD**	
		Average Typical Application Rate	Maximum Application Rate
Food	51	11 (a)	
Drinking Water			
Lower		270	69
Mid-range		49	280
Higher	Estimated ≤49%*	26	890
Aggregate	DWLOC method; not of concern	Not assessed in preliminary assessment	

* not calculated in 2000 (DWLOC method used); this estimated value represents the difference between the cPAD and food exposures, i.e. what was left in the risk cup for water after taking into account food exposures.

(a) Food estimates are highly refined and thus the average typical and maximum application rate scenarios are not applicable.

6.0 Residential (Non-Occupational) Exposure/Risk Characterization

6.1 Residential Handler Exposure

Based upon review of all chlorpyrifos registered uses, only the roach bait products can be applied by a homeowner in a residential setting; however, exposure/risk from application of the roach bait products was not quantitatively assessed because HED expects handler exposure to be negligible. The roach bait product is designed such that the active ingredient is contained within the bait station, therefore, limiting contact with the active ingredient in the product.

6.2 Residential Post-Application Exposure

Chlorpyrifos can be used in areas frequented by the general population including ant mounds on residential properties, golf courses and as an aerial and ground-based (thermal aerosol and fog machine) ULV mosquitocide applied by a public agency made in the vicinity of residential areas. As a result, individuals can be exposed by entering these areas if they have been previously treated. Short-term dermal (adults and children) and incidental oral (children only) exposures to turf following aerial and ground based ULV mosquito treatments have been assessed. Short- and intermediate-term dermal exposure/risk to adults resulting from playing golf has also been assessed. The assumptions and factors used in these risk calculations are consistent with current HED policy for completing residential exposure assessments (i.e., *Draft SOPs for Residential Exposure Assessment*). In addition to these factors, HED has used turf transferable residue (TTR) data from a chemical-specific turf study (MRID 44829601). Post-application exposure from residential ant mound treatment (applied by professional only) was not quantitatively assessed because contact with the mound is not anticipated.

A quantitative residential post-application acute inhalation exposure (spray drift) assessment was also conducted for ground and aerial ULV mosquitocide application. The assessment of residential post-application inhalation was conducted under the assumption that people may be present in the residential setting during the actual ULV application (ground and aerial). This inhalation scenario is anticipated to be an acute event. In contrast, dermal and incidental oral exposures from ULV applications (due to the subsequent settling of airborne residues on turf) are anticipated to be short-term in duration because the potential for exposure extends beyond the application event. For these reasons, residential acute inhalation estimates from ULV application have been presented (Table 21and Table 22) but not aggregated with the other routes of exposure assessed. While the assessment of post-application inhalation from the mosquitocide use has been included under the residential post-application section, it may be more accurately characterized as a spray drift exposure.

Chemical-specific data for mosquito uses are not available. Therefore the equations and assumptions for these scenarios were taken from the *Draft SOPs for Residential Exposure Assessment.* In addition to the use of the Residential SOPs, the unique nature of the mosquito control uses requires additional information to determine the deposition rate of chlorpyrifos (i.e., the amount deposited on residential turf). Deposition rates for ground-based foggers were derived from non-chemical specific studies (Moore *et al,* 1993*;* Tietze *et al*, 1994). In order to calculate deposition and breathing level air concentration from aerial ULV applications, HED

used *AgDRIFT* (V 2.01) which is the model that was developed as a result of the efforts of the *Spray Drift Task Force (SDTF).* Inhalation exposure from ground based ULV treatment was assessed by assuming that the entire active ingredient applied to a 1 acre area is airborne and available to be inhaled by a child or adult.

Risks were calculated using the Margin of Exposure (MOE) approach, which is a ratio of the body burden to the toxicological endpoint of concern. Exposures were calculated by considering the potential sources of exposure then calculating dermal, inhalation and non-dietary ingestion exposures. Short-term dermal (adults and children) and incidental oral (children only) exposures to turf following aerial and ground-based ULV mosquito treatments and adults golfing on treated turf were calculated. In addition, acute inhalation exposures to adults and children were estimated from aerial and ground ULV mosquitocide applications. Detailed assumptions and equations used to estimate exposure and risks can be found in W. Britton, 6/27/11, D388165, *Chlorpyrifos: Occupational and Residential Exposure Assessment*.

Estimated short-term adult and child dermal and child incidental oral exposure to turf following aerial and ground mosquito treatments do not exceed the level of concern (i.e. MOEs are ≥ 100). Combined child exposure estimates (dermal and incidental oral) to turf following aerial mosquito treatment result in risk estimates of concern; however, combined risk estimates following ground treatment are not of concern. Acute adult and child inhalation (spray drift) exposure following aerial mosquito treatment results in risk estimates that are not of concern (i.e. MOEs are ≥ 30), but risk estimates are of concern following ground treatment.

Adult dermal exposure from golfing does not exceed the level of concern (i.e. MOEs are ≥ 100) using any of the transferable residue (TTR) region-specific data for the emulsifiable concentrate formulation at the 1.0 lb ai/A, or 0.25 application rates.

Table 19 Adult and Child Short-term Risks (MOEs) from Residential Post-application Exposure to Turf Following Aerial ULV Mosquito Treatments At 300 Foot Spray Release Height (LOC is an MOE = 100)

Adult	
Dermal	430
Children 3 to < 6	
Dermal	260
Incidental Oral	130
Combined Exposure	88

Table 20 Adult and Child Short-term Risks (MOEs) from Residential Post-application Exposure to Turf Following Ground-based ULV Mosquito Treatments At 300 Foot Spray Release Height (LOC is an MOE = 100)

Adult	
Dermal	2,200
Children 3 to < 6	
Dermal	1,300
Incidental Oral	670
Combined Exposure	440

Table 21 Adult and Child Acute Risk (MOEs) from Residential Post-application Inhalation Exposure Following Aerial ULV Mosquito Treatments At 300 Foot Spray Release Height (LOC is an MOE = 300)

Adult and Children 3 to < 6	
Inhalation	1,600

Table 22 Adult and Child Acute Risk (MOEs) from Residential Post-application Inhalation Exposure Following Ground ULV Mosquito Treatments (LOC is an MOE = 300)

Adult and Children 3 to < 6	
Inhalation	17

Table 23 Adult Estimated Short- and Intermediate-term Risk (MOEs) from Post-application Golfing Exposure to Chlorpyrifos Treated Golf Course Turf (MRID 44829601)

Application Rate - 1.0 lb ai/A		
State	**Emulsifiable Concn.**	**Granular**
CA	830	960
IN	1,200	NA
MS	710	NA
Application Rate – 0.25 lb ai/A		
State	**Emulsifiable Concn.**	**Granular**
CA	3,300	3,800
IN	4,600	NA
MS	2,800	NA

HED has relied upon the Draft SOPs for Residential Exposure Assessment for all residential scenarios assessed. The data used in the chlorpyrifos residential post-application exposure assessment represent the best exposure data and approaches that are currently available. To the extent possible, HED has used chlorpyrifos-specific data such as the TTR data used for assessment of exposure to treated golf course turf. Chemical-specific data for aerial and ground based ULV mosquito uses are not available. For ground based ULV application, HED used data

from studies conducted to measure off site deposition from these applications. Data similar to that for ground applications were not available to determine aerial deposition. In order to calculate chlorpyrifos deposition on turf and air concentration at breathing level from aerial ULV applications, HED used the *AgDRIFT* (V 2.01) model. Once the deposition input was identified, HED used the high-end equations and assumptions from the *Draft SOPs for Residential Exposure Assessment* to assess dermal exposure to turf and inhalation exposure from mosquito applications. Although the SOPs were initially developed for direct turf applications, the models are used in this assessment to determine if there is a potential concern using a conservative, screening level approach.

HED believes that the values presented in this assessment represent the highest quality results that could be produced based on the currently available post-application exposure data. The quality of individual inputs should be considered when interpreting the risk results. It is difficult to ascertain where, on a distribution, the calculated values fall because the distributional data for exposure, residue dissipation and many other parameters are unrefined. HED does believe, however, that the risks represent conservative estimates of exposure because maximum application rates are used to define residue levels upon which the calculations are based. Additionally, estimates are thought to be conservative even when measures of central tendency (e.g., most transfer coefficients are thought to be central tendency) are used because values that would be considered to be in the lower percentile aspect of any input parameter have not been used in the calculations.

6.3 Residential Bystander Post-application Inhalation Exposure

Recently, the Agency has begun exploring the development of an approach for assessing inhalation exposure resulting from the field volatilization of conventional pesticides. The Agency has sought expert advice and input on these issues from its Federal Insecticide, Fungicide, and Rodenticide Act Scientific Advisory Panel in December 2009. More information on pesticide volatilization can be found on the Agency's website at http://www.epa.gov/opp00001/about/intheworks/volatilization.htm.

The Agency has developed a preliminary bystander volatilization inhalation exposure assessment for chlorpyrifos using currently available inhalation toxicity and air monitoring data. There are 15 available chlorpyrifos air monitoring studies (brief study summaries available in W. Britton, 6/27/11, D388165, *Chlorpyrifos: Occupational and Residential Exposure Assessment*). These include:

- 2 application site studies done in Tulare and Lompoc Counties, CA by the California Air Resource Board (CARB), and
- 13 ambient air studies
    - 2 conducted in North Central and Yakima Valley, OR by the University of Washington Department of Environmental and Occupational Health Sciences; and
    - 11 conducted by Pesticide Action Network North America (PANNA), two in Cowiche and Tieton, WA, and nine in Lindsay, CA.

Application site air monitoring refers to the collection of air samples around the edges of a treated field during and after a pesticide application. Samples are generally collected for short intervals (e.g., < 8 hours), for at least the first day or two after application with subsequent samples increasing in duration. In this type of study, it is typically known when an application occurred, the equipment used for the application, and the application rate. Application site monitoring data represents an exposure to vapors at or near the field edge resulting from an application.

Ambient air monitoring typically is focused on characterizing the airborne pesticide levels within a localized airshed or community structure of some definition (e.g., city, township, or municipality). This type of monitoring effort also can be focused on capturing chronic background levels or other temporal characteristics of interest such as focusing on seasonal pesticide use patterns. Typically, samples are taken for 24 consecutive hours and collected at the same site over an extended period of time (e.g., several weeks or months). In contrast to application site air monitoring, information on the precise timing and location of pesticide applications are rarely collected in ambient air monitoring studies. However, this does not mean that an application did not occur near an ambient sampler during the monitoring period

HED has assessed residential bystander exposure to chlorpyrifos based on the available ambient and application site air monitoring data Table 24. The chlorpyrifos bystander volatilization inhalation exposure assessment includes acute and short-/intermediate-term exposure scenarios. The acute scenario compares the maximum air concentration detected in the monitoring studies to the acute HEC. The short-/intermediate-term scenario compares the arithmetic mean chlorpyrifos air concentration from several monitoring studies to the short -term HEC.

EPA has assessed residential bystander exposure from field volatilization of applied chlorpyrifos based on the available *ambient* and *application site* air monitoring data. Of the 24 acute *ambient* air concentrations assessed, 4 result in risk estimates exceeding the level of concern (i.e. MOEs are < 300). No short-/intermediate-term *ambient* data assessed result in risk estimates of concern (i.e. MOEs are > 30). Of the 5 acute *application site* air concentrations assessed, 3 resulted in a risk estimate of concern (i.e. MOEs are < 300). Of the 5 short- and intermediate-term *application site* air concentrations assessed, 4 resulted in risk estimates of concern (i.e. MOEs are < 30).

Table 24 Chlorpyrifos Preliminary Volatilization MOE Analysis for Residential Bystanders

Study	Year of Study	Sampler/Site Location	Maximum Air Concentration (ng/m^3)	Arithmetic Mean Air Concentration (ng/m^3)	Acute MOEs[a] (LOC is an MOE = 300)	Short- / Int.-term MOEs[b] (LOC is an MOE = 30)
Ambient Air Data						
Washington DOH	2008	North Central District Ambient	21	7	29,000	850
		North Central District Receptor	607	33	1,000	180

Table 24 Chlorpyrifos Preliminary Volatilization MOE Analysis for Residential Bystanders						
Study	Year	Sampler/Site Location	Maximum	Arithmetic	Acute	Short- /
		Yakima Valley Ambient	30	9	21,000	620
		Yakima Valley Receptor	243	30	2,500	190
Lompoc County, CA (CARB)	2003	Central	8.3	1.5	19,000	3,800
		Northwest	8.4	0.84	19,000	6,800
		Southwest	6.8	0.78	24,000	7,400
		West	17	2.3	9,400	2,500
Tulare, CA (CARB)	1996	Air Resource Board	39	10	16,000	590
		Jefferson Elementary School	432	94	1,400	61
		Kaweah School	412	70	1,500	82
		Sunnyside Union Elementary School	815	52	760	110
		University of CA, Lindcove Field Station	168	39	3,700	150
Cowiche, WA (PANNA)	2006		462	155	350	37
Tieton, WA (PANNA)	2005		475	182	340	32
Lindsay, CA (PANNA)	2004	Blue House	137	54	1,200	110
Lindsay, CA (PANNA)	2004	Green House	720	120	220	50
Lindsay, CA (PANNA)	2004	Orange House	1,340	190	120	30
Lindsay, CA (PANNA)	2004	Purple House	180	48	900	120
Lindsay, CA (PANNA)	2004	Red House	90	43	1,800	130
Lindsay, CA (PANNA)	2005	Blue House	421	107	380	54
Lindsay, CA (PANNA)	2005	Green House	1,119	177	140	32
Lindsay, CA (PANNA)	2005	Orange House	561	188	290	31
Lindsay, CA (PANNA)	2005	Purple House	515	123	310	47
Application Site Data						
Washington DOH	2008	North Central District Perimeter Site	1145	153	540	37
		Yakima Valley Perimeter Site	1,002	294	620	20
Tulare, CA (CARB)	1996	North	27,700	7,706	22	1
		East	14,700	5,974	42	1
		South	25,400	5,664	24	1

a. Acute MOE = Acute HEC (62,000 ng/m^3) / Study maximum air concentration (ng/m^3).
b. Short-term MOE = Short-term HEC (5,700 ng/m^3) / Study arithmetic mean air concentration (ng/m^3).

Characterization of Bystander Risk Assessment/Uncertainties

Some of the limitations and considerations that have been identified that should be considered in the interpretation of these results include:

- Most of the data utilized in this preliminary assessment are 24-hour air samples. When these data are used, an assumption is made that an individual is exposed to the same air concentration for 24-hours every day. However, this is not always the case as real world time-activity data indicate that many parts of the population move from site to site on a daily basis (e.g., go to work and back).

- This assessment is only representative of outdoor concentrations (i.e., the exposure and risk estimates assume an individual is outdoors all the time). It does not take into account potential effects of air conditioning systems and similar air filtration systems which could potentially reduce air concentrations indoors. The Agency believes that indoor concentrations will be at worst equivalent to outdoor concentrations and may potentially be lower.

- All of the data used for this analysis have been generated in California and Washington; however, chlorpyrifos is used in many regions throughout the country. Therefore, the results based on the limited available air monitoring data were used to represent the rest of the country due to a lack of adequate information for any other region. It is unclear what potential impacts this extrapolation might have on the risk assessment. Factors such as meteorology and cultural practices may impact the overall amounts of chlorpyrifos that volatilize from a treated field as well as the rate at which it volatilizes.

- As part of the December 2009 SAP, the Agency presented their analysis of several models that could be used as screening tools to predict the air concentration and volatilization flux based on intrinsic properties and transport behaviors of pesticides. These models would allow the Agency to better represent the potential volatilization of semi-volatile pesticides across various regions of the country and thus would provide refinement to this assessment over using straight air monitoring data. The SAP provided a number of comments regarding the Agency's model analysis, including the recommendation to evaluate some additional models. The Agency is currently in the process of evaluating the SAP's comments. As appropriate, the Agency will revise the modeling approach presented to the SAP for determining the rate of volatilization (flux) for semi-volatile pesticides and for estimating air concentrations of applied pesticides in the atmosphere under varying environmental conditions. After any policies or procedures are put into place, the Agency may revisit the residential bystander exposure and risk assessment.

6.4 Spray Drift

Spray drift is a potential source of exposure to residents nearby to spraying operations. This is particularly the case with aerial application, but, to a lesser extent, could also be a potential source of exposure from the ground application method employed for chlorpyrifos. The Agency has been working with the Spray Drift Task Force, EPA Regional Offices and State Lead Agencies for pesticide regulation and other parties to develop the best spray drift management practices (see the Agency's Spray Drift website for more information at http://www.epa.gov/opp00001/factsheets/spraydrift.htm). On a chemical by chemical basis, the Agency evaluates the need for interim mitigation measures for aerial applications for placement on product labels/labeling. The Agency has completed its evaluation of the new database submitted by the Spray Drift Task Force, a membership of U.S. pesticide registrants, and is developing a policy on how to appropriately apply the data and the AgDRIFT computer model to its risk assessments for pesticides applied by air, orchard airblast and ground hydraulic methods. After the policy is in place, the Agency may seek further refinements in spray drift management practices to reduce off-target drift with specific products with significant risks associated with drift.

A quantitative residential post-application (acute) inhalation exposure (spray drift) assessment was conducted for ground and aerial ULV mosquitocide applied by a public agency made in the vicinity of residential areas (Section 6.2 above). Inhalation exposure from ground based ULV treatment was assessed by assuming that all of the active ingredient applied to a 1 acre area is airborne and available to be inhaled by a child or adult. HED used *AgDRIFT* (V 2.01), which is the model that was developed as a result of the efforts of the *Spray Drift Task Force (SDTF),* to determine residue deposition and the airborne concentration of chlorpyrifos anticipated from aerial product application.

7.0 Aggregate Exposure/Risk Characterization

In accordance with the FQPA, HED must consider and aggregate chlorpyrifos exposures and risks from three major sources: food, drinking water, and residential exposures. In an aggregate assessment, exposures from relevant sources are added together and compared to quantitative estimates of hazard (e.g., a NOAEL or PAD), or the risks themselves can be aggregated. When aggregating exposures and risks from various sources, HED considers both the route and duration of exposure.

A quantitative aggregate (food, water and residential exposures combined) assessment was not performed for this preliminary chlorpyrifos assessment. The preliminary risk estimates for water alone exceed the level of concern and are the primary driver in this assessment. Combining food and/or residential exposures with the water exposures would not be expected to have a significant impact on the resulting risk estimates for water alone. A quantitative aggregate assessment for food, water, and residential exposures will be considered during the final chlorpyrifos risk assessment.

8.0 Cumulative Exposure/Risk Characterization

Section 408(b)(2)(D)(v) of the Federal Food, Drug, and Cosmetic Act (FFDCA), as amended by the Food Quality Protection Act (1996) stipulates that when determining the safety of a pesticide chemical, EPA shall base its assessment of the risk posed by the chemical on, among other things, available information concerning the cumulative effects to human health that may result from dietary, residential, or other non-occupational exposure to other substances that have a common mechanism of toxicity. The reason for consideration of other substances is due to the possibility that low-level exposures to multiple chemical substances that cause a common toxic effect by a common mechanism could lead to the same adverse health effect as would a higher level of exposure to any of the other substances individually. A person exposed to a pesticide at a level that is considered safe may in fact experience harm if that person is also exposed to other substances that cause a common toxic effect by a mechanism common with that of the subject pesticide, even if the individual exposure levels to the other substances are also considered safe.

Chlorpyrifos is a member of the organophosphate (OP) class of pesticides. Other members of this class of pesticides are numerous and include azinphos methyl, diazinon, chlorpyrifos-methyl, dichlorvos, dicrotophos, dimethoate, disulfoton, methamidophos, methidathion, monocrotophos, naled, oxydemeton-methyl, phorate, phosmet, pirimiphos-methyl, and trichlorfon to name a few. EPA considers organophosphates to express toxicity through a common biochemical interaction with cholinesterase which may lead to a myriad of cholinergic effects and, consequently the organophosphate pesticides should be considered as a group when performing cumulative risk assessments. HED published the final guidance that it now uses for identifying substances that have a common mechanism of toxicity (FR 64(24) 5796-5799, February 5, 1999) "Proposed Guidance of Cumulative Risk Assessment for Chemicals that have a Common Mechanism of Toxicity" was made available for public comment in the Federal Register (65 FR 40644, June 30, 2000). The Agency presented this approach to the FIFRA Scientific Advisory Panel in late September, 2000. The SAP reviewed revised methods used to conduct a preliminary cumulative risk assessment for organophosphate pesticides in 2002 (US EPA, 2002), found at http://www.epa.gov/scipoly/sap/2002/index.htm.

The Agency has completed a cumulative risk assessment for OPs, (US EPA, 2001), a revised cumulative risk assessment for OPs, (US EPA, 2002), and an updated OP cumulative risk assessment (US EPA, August 2006) which can be found on the Agency's web site http://www.epa.gov/pesticides/cumulative/rra-op/. The cumulative effects of exposure to multiple OPs, including chlorpyrifos, are evaluated in those documents. OPP is in the process of evaluating the most current methods and data for suitability of use in the next version of the OP cumulative risk assessment.

9.0 Occupational Exposure/Risk Characterization

9.1 Short-/Intermediate-Term Handler Risk

Chlorpyrifos is an organophosphate insecticide currently registered for the control of various insects. Targeted pests include aphids, cockroaches, cutworms, fleas, grasshoppers, ticks, etc. Chlorpyrifos is manufactured as granular, microencapsulated, soluble concentrate/liquids, water dispersible granular in water soluble packets (WSP) and wettable powder packaged in WSP formulations, as well as impregnated paints, cattle ear tags, insect bait stations and total release foggers. Registered use sites include the following uses: food crops, including fruit and nut trees, many types of fruits and vegetables, and grain crops; and non-food crops such as forage, golf course turf, industrial sites, greenhouse and nursery production, sod farms, and wood products. Public health uses include aerial and ground-based fogger treatments to control mosquitoes. There are a wide range of application rates. HED has conducted a review of all active product labels. Table 25 and Table 26 below summarize all agricultural and non-agricultural use sites identified for chlorpyrifos under this review, respectively. Maximum application rate (lb ai/A) and application equipment for each site are also identified. Various chlorpyrifos product formulations are represented by the application rates and methods presented in the tables.

Table 25 Summary of Maximum Application Rates for Chlorpyrifos Agricultural Uses		
Crop or Target	**Maximum Application Rate (lb ai/A)**	**Application Equipment**
Alfalfa	1.0	Aerial, Chemigation, Groundboom, Tractor Drawn Spreader
Asparagus	1.0	Aerial, Groundboom
	1.5	Tractor Drawn Spreader
Beets (Table and Sugar Grown for Seed)	1.9	Aerial
Brassica Vegetable (Bok Choy, Broccoli, Broccoli Raab, Brussel Sprout, Cabbage, Cauliflower, Chinese Broccoli, Collards, Kale, and Kohlrabi)	1.0	Aerial
	2.3	Groundboom, Tractor Drawn Spreader
Carrot (Grown for Seed)	0.94	Aerial, Groundboom
Citrus Fruit	6.0 (AZ and CA), 3.5 (States other than AZ and CA)	Aerial, Airblast, Groundboom
	1.0	Tractor Drawn Spreader
	4.0	Backpack Sprayer, Handgun, Low Pressure Handwand
Clover (Grown for Seed)	1.0	Aerial, Groundboom
Corn (Field, Grown for Seed and Sweet)	1.5	Aerial, Chemigation
	3.0	Groundboom
	1.3	Tractor Drawn Spreader
Cotton	1.0	Aerial, Chemigation, Groundboom
Cranberry	1.5	Aerial, Chemigation, Groundboom
Fig (CA only)	2.0	Groundboom
Grapes	2.0	Airblast
	1.0	Backpack Sprayer, Low Pressure Handwand
Legume Vegetables (Succulent or Dried, Except for Soybeans)	1.0	Groundboom
Mint (Peppermint and Spearmint)	2.0	Chemigation, Groundboom
Onion (Dry Bulb)	1.0	Groundboom, Tractor Drawn Spreader, Handgun
Peanut	2.0	Aerial, Groundboom, Tractor Drawn Spreader
Peppers	1.0	Groundboom

Table 25 Summary of Maximum Application Rates for Chlorpyrifos Agricultural Uses		
Crop or Target	**Maximum Application Rate (lb ai/A)**	**Application Equipment**
Pineapple (Non-bearing)	1.9	Groundboom, Airblast
Radish	2.8	Aerial, Groundboom, Tractor Drawn Speader, Handgun
Radish (Grown for Seed)	0.94	Aerial, Groundboom
Rutabaga	2.3	Aerial, Groundboom, Tractor Drawn Spreader
Sorghum	1.0	Aerial, Chemigation, Groundboom
	3.3	Tractor Drawn Spreader
Soybean	1.0	Aerial, Chemigation, Groundboom
Strawberry	1.0	Aerial
	2.0	Groundboom
Sugarbeet	1.0	Aerial, Chemigation, Groundboom
	2.0	Tractor Drawn Spreader
Sugarbeet (Grown for Seed)	1.9	Aerial, Chemigation, Groundboom
Sunflower	2.0	Aerial, Groundboom
Sweet Potato	2.0	Groundboom, Tractor Drawn Spreader
Tobacco	2.0	Groundboom, Tractor Drawn Spreader
Tree Nuts (Almonds, Filberts, Pecans, Walnuts)	4.0	Groundboom, Handgun
	2.0	Aerial, Airblast
	0.03 (lb ai/gallon)	Low Pressure Handwand, Backpack Sprayer
Tree Fruit (Apples, Cherry, Nectarine, Peach, Pear, Plum, Prune, Sour Cherry)	2.0	Aerial, Airblast
	0.03 (lb ai/gallon)	Backpack Sprayer, Drench/Dip, Handgun, Low Pressure Handwand
Turnip	2.3	Groundboom, Tractor Drawn Spreader
Wheat	1.0	Aerial, Chemigation, Groundboom
	2.0	Groundboom

Table 26 Summary of Maximum Application Rates for Chlorpyrifos Non-Agricultural Uses

Crop or Target	Maximum Application Rate (lb ai/A)	Application Equipment
Ants (Fire Ant Mound, Carpenter)	0.080 (lb ai/gallon)	Backpack Sprayer, Handgun, Low Pressure Handwand
Cattle Ear Tags	0.0033 (lb ai/ ear tag)	Hand
Christmas Trees (Nurseries and Plantations, Stumps)	1.0	Airblast
	0.94	Aerial (Helicopter)
	0.03 (lb ai/gallon)	Backpack Sprayer, Handgun, Low Pressure Handwand
Golf Course Turf	1.0	Belly Grinder, Low Pressure Handwand, Push Type Spreader, Tractor Drawn Spreader, Turfgun
Grass Seed (Perennial Crops)	1.0	Groundboom
Greenhouse and Nursery Production (Bedding Plants, Containerized Ornamentals, Cut Flowers, Flowering Hanging Baskets, Pine Seedling Transplant, Potted Flowers, Ornamentals, Trees and Shrubs)	4.0	Aerial, Groundboom
	1.1	Belly Grinder, Push Type Spreader, Tractor Drawn Spreader
	1.0	Airblast
	0.16 (lb ai/gallon)	Backpack Sprayer, Handgun, Low Pressure Handwand
	0.02 (lb ai/gallon)	Soil Drench
	0.01 (lb ai/can)	Total Release Fogger
Mosquitocide (Outdoor Residential, Recreational, or Other Non-Cropland Areas)	0.010	Wide Area Aerial and Ground

Table 26 Summary of Maximum Application Rates for Chlorpyrifos Non-Agricultural Uses		
Crop or Target	**Maximum Application Rate (lb ai/A)**	**Application Equipment**
Non-crop Areas (Commercial Indoor/Outdoor Industrial Sites, Commercial Livestock Holding and Housing, Dumpsters/ Trash Areas, Food Processing Plants, Grown for Seed, Industrial Plant Site Perimeter Treatments, Manufacturing Sites, Power Utilities, Railroad Box Cars, Railroad Equipment, Road Medians, Ship Holds, Sod Farms, Telecommunications, Warehouse Sites)	1.0	Aerial, Belly Grinder, Groundboom, Push Type Spreader, Tractor Drawn Spreader
	0.11 (lb ai/gallon)	Backpack Sprayer
	0.080 (lb ai/gallon)	Handgun, Low Pressure Handwand, Paint Brush/Roller
	0.044 (lb ai/1,000 sq ft)	Shaker Container
	0.018 (lb ai/1,000 sq ft)	Open Pour Bag
Ornamentals (Cut Flowers, Industrial Buildings/Plant Sites Perimeter Treatments and Road Medians, Evergreens, Field Grown Nursery Stock, Flowers, Greenhouses, Non-bearing Fruit Trees Shrubs, Nurseries, Trees, Vines, Woody)	6.0	Belly Grinder, Push Type Spreader, Tractor Drawn Spreader
	4.0	Groundboom
	2.0	Aerial, Airblast
	0.16 (lb ai/gallon)	Backpack Sprayer, Handgun, High Pressure Handwand, Low Pressure Handwand
	0.020 (lb ai/gallon)	Drench/Dip
Roach Control Bait Stations	0.00040 (lb ai/gallon)	Hand
Sewer Manhole Walls	0.080 (lb ai/gallon)	Backpack Sprayer, Low Pressure Handwand, Paint Brush/Roller
Total Release Fogger (Greenhouse Bedding Plants, Cut Flowers, Flowering Hanging Baskets, Potted Flowers, Ornamentals)	0.010 (lb ai/container)	Hand

Table 26 Summary of Maximum Application Rates for Chlorpyrifos Non-Agricultural Uses		
Crop or Target	**Maximum Application Rate (lb ai/A)**	**Application Equipment**
Trees (Cottonwood and Poplar Trees Grown for Pulp, Conifer, Deciduous, Grown in Nurseries and Greenhouses)	2.0	Airblast, Handgun, Low Pressure Handwand, Backpack Sprayer
	1.9	Aerial
Turfgrass (Sod or Seed)	4.0	Aerial, Groundboom
	1.0	Tractor Drawn Spreader
Wood Products (Fence Posts, Industrial Sites, Landscape Timbers, Logs, Manufacturing, Pallets, Processed Wood, Right of Way, Railroad Ties, Utility Poles, Wooden Containers)	6.0	Belly Grinder, Push Type Spreader
	0.17 (lb ai/gallon)	Low Pressure Handwand
	0.080 (lb ai/gallon)	Backpack Sprayer, Handgun, Paint Brush/Roller

Under current policy, both short- term (up to 30 days) and intermediate-term (30 days up to 6 months) assessments are completed for occupational scenarios in essentially all cases, because these kinds of exposures are likely and acceptable use/usage data are not available to justify disregarding intermediate-term scenarios. Long-term exposure (essentially every working day over a year) is not anticipated based upon the use profile of chlorpyrifos.

Short- (1 to 30 days) and intermediate-term (1 to 6 months) inhalation and dermal exposure and risks were calculated for occupational handlers of chlorpyrifos for a variety of exposure scenarios at differing levels of personal protection. Occupational handler exposure estimates used three major unit exposure data sources, PHED (Pesticide Handlers Exposure Database), the Outdoor Residential Exposure Task Force (ORETF), and recently completed exposure scenario monographs as conducted and submitted by the Agricultural Handlers Exposure Task Force (AHETF). In addition to those surrogate data, two non-chemical specific exposure studies were used (MRID 44793301 and MRID 45250702).

In addition to the aforementioned studies, five chemical specific (chlorpyrifos) handler exposure (biomonitoring and passive dosimetry) studies were previously submitted in support of chlorpyrifos reregistration (MRID 42974501, Shurdut, B.A. *et al*. 1993; MRID 43138102; Honeycutt, R.C. & Day, E.W. Jr. 1994; MRID 44483501 R. F. Bischoff 1998; MRID 44739302, Knuteson *et al*. 1999; and MRID 43027901 Contardi *et al*. 1993). These studies have been reviewed and considered for use by the HED. Based on HED's review of the five chemical specific studies, a number of issues were identified which limit the utility of the available data. HED has determined that these data are most useful as a tool for comparison to the estimates generated for representative exposure scenarios using the surrogate data. That comparison is presented separately in this document. Citations and a full description of the study summaries and issues are presented in W. Britton, 6/27/11, D388165, *Chlorpyrifos: Occupational and Residential Exposure Assessment*.

Because the same adverse effect (i.e., ChEI) was seen following dermal, incidental oral and inhalation exposures, MOEs estimated for these routes of exposure can be combined. However, because the LOCs for dermal/incidental oral and inhalation routes of exposure are not the same (an MOE of 100 defines dermal/incidental oral while inhalation is defined by an MOE of 30) an aggregate risk index (ARI) was required to combine or aggregate estimated MOEs. EPA identifies as a level of concern ARIs that fail to reach or exceed the level of 1. ARIs below 1 result in a risk estimate of concern.

Of the 305 exposure scenarios assessed 134 had risk estimates that did not exceed the level of concern at some level of personal protection (i.e. ARIs are > 1). Ninety-one (91) exposure scenarios had risk estimates not of concern when engineering controls were considered. The remaining 80 scenarios resulted in risk estimates of concern (i.e. ARIs are < 1) at all levels of personal protection and engineering controls considered.

Characterization of Occupational Handler Risk Assessment/Uncertainties

The occupational handler exposure and risk assessment for chlorpyrifos is based upon an array of calculations completed for all identified exposure scenarios using the short- and intermediate-term endpoints. HED completes both short- and intermediate-term assessments for occupational scenarios in essentially all cases, because exposures of these durations are likely and acceptable use/usage data are not available to justify deleting intermediate-term scenarios. HED identified 49 different exposure scenarios which are defined based on the equipment used to make applications or the type of formulation used. Within each of these categories, different application rates and acres treated values were considered to evaluate the broad range of applications that may occur with each kind of equipment (e.g., a groundboom may be used for turf or agriculture). Finally, it should be noted that each calculation was completed at different levels of personal protection to allow for a more informed risk management decision. Even given the scope of the calculations that have already been completed, it is possible that some uses of chlorpyrifos that have not been quantitatively addressed in this document due to lack of exposure data or other information.

The data used in the chlorpyrifos occupational handler risk assessment represent the best data and approaches that are currently available. While some of the data which have been used may not be of optimal quality, they represent the best available data for the scenario in question. In many cases, the Pesticide Handlers Exposure Database (PHED) was used to develop the unit exposure values. PHED data quality varies widely from scenarios that meet guideline requirements for studies to others where a limited number of poor quality data points are available. The results for each scenario should be reviewed in the context of the quality of these data. PHED unit exposure values represent a central tendency of the data (i.e., geometric mean, median or arithmetic mean depending upon the distribution of the data). As such, the values based on the recent studies also are measures of central tendency (e.g., the geometric means were selected from each study for assessment purposes in most cases). HED used recently developed data from AHETF to assess the exposure scenarios mixing/loading liquid formulations and application of liquid sprays via open cab groundboom. HED has reviewed the data for the two studies and has confirmed that it meets study design benchmarks outlined in the AHETF Governing Document (AHETF, 2007) and is considered the most reliable data for assessing exposure and risk for these exposure scenarios. The efforts undertaken by AHETF represent a well-designed, concerted process to collect reliable, internally-consistent, and current exposure data in a way that takes advantage of and incorporates a more robust statistical design, better analytical methods, and improved data handling techniques. For the purpose of the assessment of the two exposure scenarios, HED has used the arithmetic mean unit exposure for short- and intermediate-term exposure durations as recommended in the study reviews (D373605). The AHETF scenarios were recently posted and are publically available on the EPA website as of 4/8/2011 (http://www.epa.gov/pesticides/science/handler-exposure-data.html). This new data were included in the presentation of the most current data used to assess exposure and risk for occupational pesticide handlers.

Along with the unit exposure values used in the assessment, other inputs include application rates and daily acres treated values. The application rates selected for occupational handler risk assessment represent the maximum amounts that are allowed by the label for all uses. The

application rates that were selected for use in the risk assessment were defined based on a review of all current labels. The other key input for completing handler risk assessments used for defining how much chemical can be used in a day is how much can be treated in a day which is generally expressed as the number of acres treated per day. The values used for this parameter represent the HED's most current thinking.

In addition to the key sources of information considered above, there are many underlying factors that may impact the overall results of a risk assessment. For example, the protection factors used for adding additional levels of dermal and respiratory protection may impact the overall risk picture. The factors used in this assessment by HED have been in use for many years. There are exposures monitoring issues which must be considered. For example, in many cases the data included in PHED are based on the use of cotton gloves for hand exposure monitoring which is thought by many to have the potential to overestimate exposure because they potentially retain residue more than a bare hand would over the course of a work day. Such intangible elements of the risk assessment reflect many of the hidden uncertainties associated with exposure data.

In summary, HED believes that the risk values presented in this occupational assessment represent the highest quality results that could be produced given the exposure, use, and toxicology data that are available. Risk managers and other interested parties should consider the quality of individual inputs when interpreting the results and make decisions accordingly. It is difficult to ascertain at what point on a distribution the values which have been calculated fall because the distributional data for exposure, application rates, acres treated and many other parameters are unrefined. HED does believe, however, that the risks represent conservative estimates of exposure because maximum application rates are coupled with high acreage estimates to define risk estimates that likely fall in the upper percentiles of the actual exposure distributions. Additionally, risk estimates are thought to be conservative even when measures of central tendency are combined because values that would be considered to be in the lower percentile aspect of any input parameter have not been used in the calculations.

Occupational Handler Comparison Using Biomonitoring Data

Occupational handler exposure estimates were based on surrogate data from AHETF, ORETF and PHED, as well as two non-chemical specific studies. In addition to these data, five chemical specific handler exposure studies submitted in the past in support of chlorpyrifos re-registration were reviewed and considered for use by the HED. Risk estimates have been calculated using absorbed doses (mg/kg) measured from the biomonitoring studies determined to be acceptable for quantitative risk assessment purposes. In order to characterize occupational risk estimates calculated using surrogate, passive dosimetry exposure data, HED has presented a comparative analysis of these data and biomonitoring data available for applicable exposure scenarios. Comparative estimates using chemical specific handler exposure studies are limited to the level of clothing and personal protection worn by the participants when the studies were conducted. Comparative short- and intermediate term occupational handler exposure/risk using biomonitoring and surrogate exposure data are presented in Appendix B which accompanies document D388165.

All five chemical specific exposure studies (MRID 42974501, MRID 43138102, MRID 44739302 and MRID 43027901 and MRID 44483501) were reviewed for ethical conduct. All but one (MRID 44483501) were determined to be ethically relevant to the standards of the time that the studies were conducted. In addition, all studies were reviewed as to their relevance in the current market in regard to product formulation. Based on this analysis, one study measured the mixing/loading of a wettable powder formulation which is no longer supported by the product registrant. Despite this limitation, the application of the mixed wettable powder formulation was considered for use because the formulation was mixed into a liquid form and is, therefore an acceptable surrogate. HED considered use of the four remaining handler exposure studies and weighed the strengths and weaknesses of each. A number of issues limit the utility of the studies, including: the sufficiency of sample size, PPE worn by study participants, sufficient risk mitigation is not provided (e.g., additional PPE or engineering controls), and the studies do not encompass all handler uses of the chemical.

The number of monitored workers across the four studies range from 15 to 1. HED has typically relied on the criteria set forth by the Pesticide Assessment Guideline which recommend 15 exposure measurements as a minimum for each exposure scenario. Only 1 of the 4 studies meets this criterion. For example, a mixer/loader/applicator greenhouse study (MRID 43027901) attempted to monitor 6 different greenhouse handler scenarios and, as a result was only able to collect 5 measurements for 2 exposure scenarios, 3 for another, and only 1 for each of the remaining 3 scenarios.

Workers participating in the four reviewed studies wore a wide range of clothing and personal protective equipment. All workers wore an inner dosimeter which included t-shirt and briefs used to measure the penetration of chlorpyrifos through the outer dosimeter. The outer dosimeter was typically represented either by coveralls, or long sleeved shirt and long pants. For example, in the mixing/loading for aerial applications study (MRID 44739302), participants wore chemical-resistant gloves, apron and knee high boots. In another study, mixing/loading/applying for ornamentals in greenhouses, the workers wore chemical-resistant gloves, socks, rubber boots, and protective eyewear. In this same study, participants who conducted overhead applications also wore neoprene rain paints and a rain jacket over the coveralls, a half face respirator equipped with two organic vapour cartridges and pre-filters, and a face shield. The study authors attempted to account for the additional PPE through means of assigned penetration factors. It is possible that the additional PPE, despite correction, affect passive and biomonitoring results by reducing worker exposure to chlorpyrifos that would have otherwise deposited on the inner or outer dosimeters in their absence and likewise, result in an assessment which potentially underestimates human health exposure/risk for the exposure scenario. This is of particular concern in the greenhouse study because the personal protective equipment worn by study participants making overhead applications exceeds current labelled requirements.

Because the four available (ethically acceptable) studies were conducted with study participants wearing a specific combination of clothing and PPE, the utility of the data are limited to assessment of occupational handler exposure/risk which is represented by that level of clothing or personal protection. For example, in the mixing/loading for airblast application study (MRID 43138102) workers wore inner dosimeters (t-shirts and briefs), short sleeved shirt, long pants and

outer dosimeters (coveralls), chemical resistant gloves and half-face respirator. Therefore, data from the study would be limited to the assessment of occupational handlers mixing/loading liquids with double layer clothing, gloves and PF10 respirator. Furthermore, since the available exposure studies are specific to particular handler activities and formulations (e.g., mixing/loading for liquid formulations) the utility of the data are limited to these parameters.

In view of the issues outlined, HED has determined that of the four available studies reviewed, three should be considered for quantitative risk assessment purposes (MRIDs 42974501, 43138102, and MRID 44739302). The mixing/loading liquids for aerial applications study (MRID 44739302) was used to present a comparative biomonitoring estimate for the mixing/loading liquids for aerial applications exposure scenario at double layer clothing, gloves and no respirator level of personal protection. The mixing/loading liquids for and airblast application study (MRID 43138102) was used to present a comparative estimate for the mixing/loading liquids for airblast application and airblast application exposure scenario at single layer clothing, gloves and PF10 respirator level of personal protection. Study MRID 42974501 measured exposure from the mixing/loading and application of a wettable powder formulation and mixing/loading of a liquid formulation for ground boom application. Because the wettable powder formulation is no longer supported, only the subsequent liquid application by ground boom exposure data was used to present a comparative estimate at single layer, gloves and PF10 respirator level of personal protection.

Appendix B, which accompany document D388165 present the comparative short- and intermediate-term occupational handler exposure/risk estimates, respectively. Risk estimates compare the level of personal protection measured in biomonitoring exposure studies and the corresponding level estimated using surrogate exposure data.

In an effort to characterize occupational handler risk estimates calculated using both surrogate data and passive dosimetry (chemical specific handler) exposure data, HED has presented a comparative analysis of these for applicable exposure scenarios. Comparative risk estimates were calculated using absorbed doses measured from chemical specific handler studies determined to be acceptable for quantitative risk assessment purposes. The comparison of handler risk estimates was limited based on the level of clothing and personal protection worn by the participants when the biomonitoring studies were conducted.

Of the 4 exposure scenarios compared, 3 (mixing/loading liquids for airblast application, airblast applications, and groundboom applications) result in biomonitoring estimates of greater risk potential than those estimated using surrogate data (i.e., the estimated MOEs are lower). The analysis of the exposure scenario, mixing/loading liquids for aerial application, results in reduced risk potential (a 3.8X reduction in MOE estimate). Because a number of issues were identified which limit the utility of the available biomonitoring data, HED has determined that these data are best suited for characterization of the estimates calculated for representative exposure scenarios using the surrogate data.

Commercial Seed Treatment

Occupational handlers may experience short- and intermediate-term (dermal and inhalation) exposure to chlorpyrifos while performing seed treatment activities in commercial settings. In addition, occupational secondary handlers may experience short- and intermediate-term exposure while planting chlorpyrifos-treated seeds. No chemical-specific handler exposure data were submitted in support of this use pattern. In order to assess commercial seed treatment and seed planting activities, unit exposure data were taken from HED ExpoSAC Policy 14: SOPs for Seed Treatment. The amount of active ingredient handled depends on the application rate (lb ai/lb seed) and the pounds of seed treated in a day (or the pounds of seed that can be planted in a day), all of which vary depending upon the seed type. Values for the amount of seed treated and planted per day were obtained from HED ExpoSAC Policy 15.

Commercial seed treatment exposure and risk estimates were calculated using the formulas and MOE approach used for other occupational handler scenarios. It should be noted that for commercial seed treatment, the application rate is presented in units of lbs ai/lb seed and daily amount handled is presented in units of lbs seed/day.

The majority, 61 of 64, occupational handler seed treatment exposure scenarios assessed (combined dermal and inhalation) resulted in risk estimates which were not of concern (i.e. ARIs are > 1) at some level of personal protection. The remaining 3 exposure scenarios resulted in an ARI < 1 at all level of personal protection considered and, therefore, are of concern. All seed planter (secondary handler) combined short- and intermediate-term dermal and inhalation exposure scenarios assessed resulted in an ARI > 1 at some level of personal protection and, therefore, do not present risk estimates of concern.

Complete results for short- and intermediate-term commercial seed treatment and secondary handler exposure is presented in Appendix C which accompanies document D388165.

9.2 Short-/Intermediate-Term Post-Application Risk

9.2.1 Dermal Post-Application Risk

HED has assessed short- and intermediate term occupational post-application dermal exposure and risk for any crops which reentry into an area previously treated with chlorpyrifos is anticipated. The assessment was completed using 7 chemical-specific registrant submitted DFR studies. The studies, which encompass the use of five different formulations and twelve different crops, have been extrapolated to other groups based on the nature of the crop and application method and used to calculate risks for post-application workers in every region of the county. The results of the post-application exposure and risk assessment are summarized in Table 27 below. A full presentation of post-application exposure and risk including estimates calculated for low, medium and high contact activities and resulting REIs reference Appendix E which accompanies D388165.

The MOEs estimated for liquid spray and granular formulation reentry are not of concern (i.e., an MOE ≥ 100) in the range of 0 to 4 days for lower to medium exposure activities and 0 to 8 days

for high exposure activities, with the greater majority falling between 0 to 4 days when all exposure activities are considered. HED also estimated the MOEs for reentry into microencapsulated and total release fogger formulation treated greenhouses. These estimates range from 0 to > 35 days after treatment (the completion of the monitoring period) for all exposure activities considered.

Table 27 Results of the post-application exposure and risk assessment

Crop Group	Crop	App. Rate (lbs ai/A)	DFR Data Source	DFR Study Location	Growing Region	Estimated REI Range (days) (Dermal LOC = 100)
Berry: Low	Strawberry	1.0	MRID 42974501 (cauliflower WP)	AZ	3, 5, 10 and 12	0 - 2
	Cranberry	1.5			1, 5, 10 and 12	0 - 4
Field and Row Crops: Low to Medium	Clover (Grown for Seed)	1.9	MRID 44748102 (sugar beet EC)	MN	5	1
				OR	11	1
	Perennial Grass Seed Crops	1.0	MRID 44748102 (sugar beet EC)	MN	5	1
				OR	11	1
	Alfalfa	1.0	MRID 44748102 (cotton EC)	TX	5 and 7	1
	Cotton	1.0	MRID 44748102 (cotton EC)	CA	10	0 – 3
				MS	4	0 - 1
				TX	6 and 8	0 - 1
	Peppermint/ Spearmint	2.0	MRID 44748102 (sugar beet EC)	MN	5	0 - 1
				OR	11	0 - 1
	Wheat	1.0	MRID 44748102 (sugar beet EC)	CA	8	1
				MN	5 and 7	1
	Soybean	1.0	MRID 44748102 (cotton EC)	MS	4 and 5	0 - 1
	Sugar Beet	1.0	MRID 44748102 (sugar beet EC)	CA	10	0 - 1
				MN	5	0 - 1
				OR	11	0 - 1
Field and Row Crops: Tall	Corn: Sweet	1.5	MRID 44748102 (sweet corn EC)	IL	1 and 5	0 - 3
				MN	1 and 5	0 - 3
				OR	11	0 - 2
	Corn: Sweet	1.0	MRID 44748102 (sweet corn EC)	IL	1 and 5	0 - 3
				MN	1 and 5	0 - 3
				OR	11	0 - 2
	Corn: Field, Including Grown for Seed	1.5	MRID 44748102 (sweet corn EC)	IL	5	0 - 3
				MN	5	0 - 3

Crop Group	Crop	App. Rate (lbs ai/A)	DFR Data Source	DFR Study Location	Growing Region	Estimated REI Range (days) (Dermal LOC = 100)
	Corn: Field, Including Grown for Seed	1.0	MRID 44748102 (sweet corn EC)	IL	5	0 - 3
				MN	5	0 - 3
	Sorghum	1.0	MRID 44748102 (sweet corn EC)	IL	5, 6, 7 and 8	0 - 1
				MN	5, 6, 7 and 8	0 - 1
	Sunflowers	1.5	MRID 44748102 (sweet corn EC)	IL	5 and 7	1
				MN	5 and 7	1
Tree Fruit: Deciduous	Apple (Dormant and Delayed Dormant)	2.0	MRID 44748101 (apple WP)	CA	10	0 - 1
				WA	11	0 - 2
				NY	1, 2, 5	0 - 2
	Cherry (Sweet) (Dormant and Delayed Dormant)	2.0	MRID 44748101 (apple WP)	CA	10	0 - 1
				WA	11	0 - 2
				NY	5	0 - 2
	Cherry (Sour) (Dormant and Delayed Dormant)	2.0	MRID 44748101 (apple WP)	NY	1 and 5	0 - 2
	Peaches (Dormant and Delayed Dormant)	2.0	MRID 44748101 (apple WP)	CA	10	0 - 1
				NY	2	0 - 2
	Pears (Dormant and Delayed Dormant)	2.0	MRID 44748101 (apple WP)	CA	10	0 - 1
				WA	11	0 - 2
	Nectarines, Plums, Prunes (Dormant and Delayed Dormant)	2.0	MRID 44748101 (apple WP)	CA	10	0 - 1
	Apples	1.5	MRID 44748101 (apple WP)	CA	10	0 - 1
				WA	11	0 - 4
				NY	1, 2, 5	0 - 4
	Cherries (Sour)	1.5	MRID 44748101 (apple WP)	NY	1 and 5	
	Peaches (Post-harvest)	3.0	MRID 44748101 (apple WP)	CA	10	0 - 1
				NY	2	0 - 2
	Pears (Post-harvest)	2.0	MRID 44748101 (apple WP)	CA	10	0 - 1
				WA	11	0 - 2
Tree Fruit: Evergreen	Conifer Trees and Christmas Tree Plantations	1.0	MRID 43062701 (citrus EC)	CA	Any	0 - 1
	Citrus	6.0 (CA and AZ)	MRID 43062701 (citrus EC)	CA	3 and 10	0 - 2

Crop Group	Crop	App. Rate (lbs ai/A)	DFR Data Source	DFR Study Location	Growing Region	Estimated REI Range (days) (Dermal LOC = 100)
		3.5	MRID 43062701 (citrus EC)	CA	3 and 10	0 - 1
Forestry	Cottonwood/ Poplar Trees Grown for Pulp (Dormant)	2.0	MRID 44748101 (apple WP)	WA	11	2
				NY	1 and 7	2
	Deciduous Trees (Plantations and Seed Orchards)	1.0	MRID 44748101 (apple WP)	CA		1
				WA		1
				NY		1
Tree Nuts	Almonds	2.0	MRID 44748101 (almond WP)	CA (arid)	10	1
	Almonds (Dormant and Delayed Dormant)	2.0	MRID 44748101 (almond WP)	CA (arid)	10	1
	Filberts	2.0	MRID 44748101 (pecan EC)	GA	12	0
	Pecans		MRID 44748101 (pecan EC)	GA	2	0
				LA	6	0
				TX	8	0
	Walnuts		MRID 44748101 (pecan EC)	TX	10	0
	Filberts (Dormant and Delayed Dormant)	2.0	MRID 44748101 (pecan EC)	GA	12	0
	Walnuts (Dormant and Delayed Dormant)		MRID 44748101 (pecan EC)	TX	10	0
Ornamentals/ Nurseries (Outdoor Only)	Deciduous Trees in Nurseries and Orchards Except Apples (Dormant and Delayed Dormant) Non-bearing Apple Trees	2.0	MRID 44748101 (apple WP)	CA	10	0
				WA	11	1
				NY	1, 2, 5	1
Ornamentals/ Nurseries (Outdoor Only)	Non-bearing Citrus, Tree Nut and Cherry	4.0	MRID 43062701 (citrus EC)	CA	2, 3, 6, 8, 10, 12	0
	Non-bearing Peach and Nectarine Trees	3.0	MRID 44748101 (apple WP)	CA	10	1
				NY	2	1

Crop Group	Crop	App. Rate (lbs ai/A)	DFR Data Source	DFR Study Location	Growing Region	Estimated REI Range (days) (Dermal LOC = 100)
	Conifers in Nurseries	1.0	MRID 43062701 (citrus EC)	CA	Any	0
Field and Row Crops: Low to Medium (Outdoor Only)	Ornamentals	2.0	MRID 44748102 (sugar beet EC)	CA	Any	0 - 5
				MN	Any	0 - 6
				OR	Any	0 - 2
Vegetable: Root and Tuber	Carrot (Grown for Seed)	0.94	MRID 44748102 (sugar beet EC)	CA	10	0 – 1
				MN	3 and 5	0 – 1
	Radish (Grown for Seed)	0.94	MRID 44748102 (sugar beet EC)	MN	3 and 5	0 – 1
Vegetable: Fruiting	Pepper	1.0	MRID 44748102 (cotton EC)	CA	9 and 10	0 - 2
				MS	2 and 3	0 - 1
				TX	8	0 - 1
Vegetable: Head and Stem Brassica	Broccoli, Brussel Sprout and Cauliflower	1.0	MRID 42974501 (cauliflower WP)	AZ	10	0 - 8
	Cabbage		MRID 42974501 (cauliflower WP)	AZ	1, 2 and 5	
Vegetable: Leafy	Bok Choy	1.0	MRID 42974501 (cauliflower WP)	AZ	3 and 10	0 - 4
	Collards, Kale, Kohlrabi	1.0	MRID 42974501 (cauliflower WP)	AZ	2	
Stalk and Stem: Vegetable	Asparagus	1.0	MRID 44748102 (sugar beet EC)	CA	10	0 – 1
				MN	5	0 - 1
				OR	11	0 - 1
	Non-bearing Pineapple	1.9	MRID 44748102 (cotton EC)	MS	13	0 - 1
Vine/ Trellis	Grapes (Dormant and Delayed Dormant) Grapes (Post-harvest and Prior to Budbreak)	2.0	MRID 43062701 (citrus EC)	CA	10	0
Turf	Turf for Sod and Seed	4.0	MRID 448296-01 (turf EC and WP)	CA	10	1
				IN	5	1
				MS	2 and 6	1
	Turf for Golf Course	1.0	MRID 448296-01 (turf EC and WP)	CA	10	0
				IN	5	0

Crop Group	Crop	App. Rate (lbs ai/A)	DFR Data Source	DFR Study Location	Growing Region	Estimated REI Range (days) (Dermal LOC = 100)
				MS	2 and 6	0
Field and Row Crops: Low to Medium	Soybeans	1.0	MRID 44748102 (sweet corn G)	IL	4 and 5	0
	Sugar Beet	2.0	MRID 44748102 (sweet corn G)	IL	5	0
				OR	10 and 11	0 - 1
	Peanuts	4.0	MRID 44748102 (sweet corn G)	IL	2 and 6	0 - 1
Field and Row Crops: Tall	Corn: Sweet	1.0	MRID 44748102 (sweet corn G)	IL	1 and 5	0
				OR	11	0
	Corn: Field and Grown for Seed	1.0	MRID 44748102 (sweet corn G)	IL	5	0
Nursery	Woody Ornamentals (In Container and Field Grown)	6.0	MRID 44748102 (sweet corn G)	IL	Any	0
				OR		
Turf	Turf for Sod or Seed	1.0	MRID 448296-01 (turf G and fertilizer)	CA	Any	0
	Golf Course					0
Greenhouse (Microencap. Formulations)	Commercial Ornamentals, Greenhouse Production: Bedding Plants, Cut Flowers, Flowering Hanging Baskets, Potted Flowers, Ornamentals, Trees and Shrubs	1.4	MRID 46722702 (smooth ornamentals ME)	MO	Any	0 to > 35
Greenhouse (Total Release Fogger and. Liquid Concentrate Formulations)	Ornamentals	2	MRID 46722701 (hairy ornamentals ME)	MO	Any	18 to > 30
	Commercial Ornamentals, Greenhouse Production: Bedding Plants, Cut Flowers, Flowering Hanging Baskets, Potted Flowers, Ornamentals, Trees and Shrubs	0.01 lb ai/ fogger/ 3,000 sq ft 0.15 lb ai/A	MRID 46722701 (hairy ornamentals ME)	MO	Any	2 - 22

Characterization of Occupational Post-Application Risk Assessment

The occupational post-application exposure and risk assessment for chlorpyrifos is based upon an array of calculations completed for 15 different crop groups. These unique crop groupings are defined essentially based on the nature of the crop where a work activity would take place. Within each of these groupings, ranges of transfer coefficients were considered to reflect differences in exposures that would be associated with the variety of cultural practices required to produce the crop/product. Transfer coefficients are used "generically" to allow for estimation of exposure for any pesticide active ingredient using estimates for exposure time and the concentration of residue the workers will contact that is specific to the pesticide of interest. The Agency has adopted a method of clustering groups, crop growth stages, and post-application activities into groups that are expected to result in comparable exposure. Chlorpyrifos post-application exposures were estimated over subsequent days after application to reflect residue dissipation over time in the environment and to allow for a more informed risk management decision.

The exposure data used in the chlorpyrifos post-application exposure and risk assessment represent the best data and approaches that are currently available. The latest HED transfer coefficients have been used to complete the assessment, as referenced from the Science Advisory Council for Exposure (ExpoSAC) Policy Number 3.2: Agricultural Transfer Coefficients (5/5/11). Most of the transfer coefficient values in Policy 3.2 are based on the work of the Agricultural Reentry Task Force (ARTF). The choice of post-application activities studied by the ARTF, as well as the subsequent assignment of transfer coefficients derived from these studies to non-monitored post-application activities was developed with input from both the ARTF and HED staff Agency and reviewed by the FIFRA SAP in 2008. It is possible that there are exposure scenarios not addressed by HED either due to the lack of appropriate exposure data or because the transfer coefficient model is not appropriate or little or no foliar contact is associated with a specific activity. Furthermore, unlike the vast majority of crop-activity combinations listed under the Transfer Coefficient Table in Policy 3.2, some common agricultural activities do not follow the standard "foliar-based" transfer coefficient methodology. This should not be interpreted to mean that there is no potential exposure from these activities but rather that "foliar-based" transfer coefficients are not applicable to evaluate worker exposure. For example, the crop-activity combinations of mechanical windrowing, mechanical sweeping and dormant hand pruning for the "nut tree" crop grouping are standard cultural practices; however, do not follow the standard transfer coefficient methodology.

HED completed the assessment of occupational post-application exposure and risk to chlorpyrifos using 7 chemical-specific DFR studies submitted by the registrant in support of the re-registration of chlorpyrifos. The studies, which encompass the use of five different formulations and twelve different crops, have been extrapolated to other groups based on the nature of the crop and application method and used to calculate risks for post-application workers in every region of the county. It is standard practice for the Agency to use these kinds of studies in this manner. Furthermore, it is possible that the use of the 7 chemical specific DFR studies to represent all crops and regions within the country could lead to results that do not reflect actual use practices and conditions in some parts of the country. Furthermore, the extrapolation of DFR data from one crop may not represent precisely the dissipation of another.

For example, DFR data which measured the dissipation of chlorpyrifos from cotton after application of an emulsifiable concentrate were used to represent dissipation of chlorpyrifos from soybeans which like cotton, are classified in the low/medium field row crop grouping. HED assumes that residue dissipation monitored in available studies approximates residues from like crops, but the extent that these residues might be an under- or over-estimate is unknown. Finally, DFR data for several crops were conducted in multiple states reflective of the regions of the country where the crops are typically grown and chlorpyrifos is used. HED has presented all state-specific DFR data for each crop under the assumption that these data accurately reflect dissipation anticipated in the different regions of the country (e.g., the subtropical Southeastern U.S. and the semi-arid climate of the Central Valley of California). HED has considered available use and usage information in development of the occupational post-application assessment and has refined the use of available region-specific DFR data to those areas of the U.S. where chlorpyrifos usage occurs.

In summary, the Agency believes that the risk values presented in this post-application assessment represent the highest quality results that could be produced given the exposure, use, and toxicology data that are available. Risk managers and other interested parties should consider the quality of individual inputs when interpreting the results and make decisions accordingly. It is difficult to determine where on a distribution the values which have been calculated fall because the distributional data for exposure, residue dissipation and many other parameters are unrefined. The Agency does believe, however, that the risks represent conservative estimates of exposure because maximum application rates are used to define residue levels upon which the risk calculations are based and most maximum application rates exceed what is assumed to be typical.

9.2.2 Inhalation Post-application Risk

There are multiple potential sources of post-application inhalation exposure to individuals performing post-application activities in previously treated fields. These potential sources include volatilization of pesticides and resuspension of dusts and/or particulates that contain pesticides. The Agency sought expert advice and input on issues related to volatilization of pesticides from its Federal Insecticide, Fungicide, and Rodenticide Act Scientific Advisory Panel (SAP) in December 2009, and received the SAP's final report on March 2, 2010 (http://www.epa.gov/scipoly/SAP/meetings/2009/120109meeting.html). The Agency is in the process of evaluating the SAP report as well as available post-application inhalation exposure data generated by the Agricultural Reentry Task Force and may, as appropriate, develop policies and procedures, to identify the need for and, subsequently, the way to incorporate occupational post-application inhalation exposure into the Agency's risk assessments.

However, based on the Agency's current practices, a quantitative post-application inhalation exposure assessment is not typically performed for a chemical when it is characterized by low acute inhalation toxicity (Toxicity Category III and IV) and low vapor pressure. Chlorpyrifos does not fit into these categories as it is classified as Toxicity Category II for inhalation toxicity and has a moderate vapor pressure of 1.9×10^{-5} mm Hg at 25º C. The inhalation exposure potential from occupational/commercial post-application activities may be elevated based upon these criteria. A quantitative occupational post-application inhalation exposure assessment was

not performed for chlorpyrifos; however, an inhalation exposure assessment was performed for occupational/commercial handlers. It is expected that while many of these handler inhalation exposure estimates are of concern to HED, exposure and risk from occupational post-application inhalation would be of no greater concern than occupational handler inhalation estimates.

Chlorpyrifos can be used in indoor facilities as well as agricultural/commercial outdoor uses. Indoor use sites for chlorpyrifos include greenhouse use, indoor commercial uses (e.g., warehouses, indoor industrial sites) and commercial seed treatment facilities. HED has not assessed post-application inhalation exposure for greenhouses due to requirements for high air exchange rates and ventilation regulations. The Worker Protection Standard for Agricultural Pesticides contains requirements for protecting workers from inhalation exposures during and after greenhouse applications through the use of ventilation requirements [40 CFR 170.110, (3) (Restrictions associated with pesticide applications)]. Furthermore, HED assumes that commercial applicators do not typically return to the treated areas after an indoor use site pesticide application and thus an occupational post-application inhalation exposure assessment was not performed for commercial applicators. Seed treatment assessments provide quantitative inhalation exposure assessments for seed treaters and secondary handlers (i.e. planters). It is expected that these exposure estimates would be protective of most post-application inhalation exposure scenarios.

9.2.3 ORE Evaluation of Chlorpyrifos-oxon

HED has considered the exposure potential for occupational and residential exposure to chlorpyrifos-oxon. Workers re-entering an environment previously treated with chlorpyrifos (occupational post-application) and the general population residing near chlorpyrifos application sites (bystanders) could potentially be exposed to the oxon as chlorpyrifos is metabolized in the environment. Dermal exposure to the oxon could occur through contact with chlorpyrifos treated surfaces and inhalation exposure through airborne oxon. However, the likelihood of exposure to the oxon is slight due to its rapid deactivation to TCP in the environment. In an effort to further explore the potential for oxon exposure, HED has researched and reviewed all available information sources. Chlorpyrifos and chlorpyrifos-oxon were measured in several air monitoring studies. A search of open literature resulted in 4 metabolism studies which measured whole fruit and leaf surface residue of chlorpyrifos and chlorpyrifos-oxon. [See W. Britton, 6/27/11, D388165, *Chlorpyrifos: Occupational and Residential Exposure Assessment*, Section 4 for a full discussion of study results and conclusions.]

The Agency has considered the potential for occupational and residential exposure to chlorpyrifos-oxon. Workers re-entering an environment previously treated with chlorpyrifos (occupational post-application) and the general population residing near chlorpyrifos application sites (bystanders) could potentially be exposed to the oxon as chlorpyrifos is degraded in the environment. Dermal exposure to the oxon could occur through contact with chlorpyrifos treated surfaces and inhalation exposure through airborne oxon. However, the likelihood of exposure to the oxon is slight due to its rapid deactivation to TCP (3,5,6-trichloro-2-pyridinol). In an effort to further explore the potential for oxon exposure, EPA has researched and reviewed all available information sources. Based upon this review, EPA intends to require additional studies to

address uncertainties regarding the formation of chlorpyrifos-oxon in the air post-application and its formation and decay in greenhouses.

Dermal exposure to the oxon on foliar surfaces from reentry into an outdoor environment previously treated with chlorpyrifos is not anticipated and, therefore, has not been assessed. However, HED is concerned, based on study results, that the formation of the oxon may be greater and its deactivation slower in greenhouses when compared to the outdoor environment and that an assessment may be needed for exposure to the oxon in greenhouse settings. In order address these uncertainties and more accurately address the risk potential for exposure from occupational reentry into greenhouses treated with chlorpyrifos, HED requires a study to measure chlorpyrifos and oxon residues on leaf surfaces following treatment with a liquid formulation of chlorpyrifos in greenhouses.

9.2.4 Comparison of the Chlorpyrifos 2000 Risk Assessment and 2011 Preliminary Risk Assessment

Table 28 and Table below present a range of resulting occupational handler risk estimates (MOEs) for both the current preliminary (2011) chlorpyrifos assessment and the June 2000 chlorpyrifos assessment for comparison purposes. The range represents a low, medium, and high exposure scenario. Also presented is a range of personal protection (single layer/gloves, double layer/gloves, and engineering controls). Table 28 shows the short-term and intermediate –term dermal risk estimates and Table 29 shows the short-term and intermediate –term inhalation risk estimates.

The dermal handler risk estimates remain unchanged between the 2000 and 2011 assessments since the dermal PoD is the same (NOAEL of 5 mg/kg/day from a dermal study). The 2008 SAP concurred with the selection of this PoD for assessing dermal scenarios.

The inhalation PoD in 2000 was 0.1 mg/kg/day (NOAEL based on inhalation studies). That same PoD is used in the current assessment except that it has been converted to an HEC (human equivalent concentration). This resulted in the reduction of the default database uncertainty factor for interspecies extrapolation from a 10x to a 3x. Thus the level of concern MOE for this assessment is 30 (compared to 100 in 2000). In addition the NOAEL was corrected to account for an 8 hour workday because worker exposure is expected to occur during the course of an average workweek (8 hours/day and 5 days/week; animals were exposed 6 hours a day in the study). The inhalation handler risk estimates have changed since the 2000 assessment. This can be mainly attributed to the use of the HEC in the preliminary assessment.

Note that the actual dermal and inhalation MOEs presented in the 2000 assessment may differ somewhat than those presented here since some of the exposure assumptions used today may vary due to refinements made since 2000. The 2011 exposure assumptions were compared to the 2000 PoD for illustrative purposes only.

Table 28 Comparative Analysis of Occupational Handler Exposure Estimates Considering 2000/2011 Dermal PoDs Using Low, Medium and High Level Representative Scenarios

Level	Exposure Scenario	Target	App. Rate[a] (lb ai/A)	Level of Personal Protection – Risk Estimates (MOE)		
				Single Layer[1], Gloves	Double Layer[2], Gloves	Engineering Control
Risk Estimates with 2011 Assessment Dermal PoD (5 mg/kg/day)						
Low	Groundboom Applications	Non-Crop Areas (Industrial Plant Sites, Road Medians, and Sod Farms), Turfgrass	0.25	1,100	1,400	3,400
Medium	Mixing/Loading Liquids for Groundboom Application	Asparagus, Brussel Sprouts, Sugarbeet	1.0	120	150	510
High	Airblast Applications	Citrus (CA and AZ)	6.0	6	11	77
Risk Estimates with 2000 Assessment Dermal PoD (5 mg/kg/day)						
Low	Groundboom Applications	Non-Crop Areas (Industrial Plant Sites, Road Medians, and Sod Farms), Turfgrass	0.25	1,100	1,400	3,400
Medium	Mixing/ Loading Liquids for Groundboom Application	Asparagus, Brussel Sprouts, Sugarbeet	1.0	120	150	510
High	Airblast Applications	Citrus (CA and AZ)	6.0	6	11	77

1. Single layer (long-sleeve shirt, long pants, shoes, socks), chemical resistant gloves
2. Double layer (single layer clothing with the addition of coverall), chemical resistant gloves

Table 29 Comparative Analysis of Occupational Handler Exposure Estimates Considering 2000/2011 Inhalation PoDs Using Low, Medium and High Level Representative Scenarios

Level	Exposure Scenario	Target	App. Rate[a] (lb ai/A)	Level of Personal Protection – Risk Estimates (MOE)			
				No Respirator	PF5[1] Respirator	PF10[2] Respirator	Engineering Control
Risk Estimates with 2011 Assessment Inhalation PoD (0.56 mg/kg/day) – LOC is an MOE = 30							
Low	Groundboom Applications	Non-Crop Areas (Industrial Plant Sites, Road Medians, and Sod Farms), Turfgrass	0.25	5,800	29,000	58,000	46,000
Medium	Mixing/ Loading Liquids for Groundboom Application	Asparagus, Brussel Sprouts, Sugarbeet	1.0	2,200	11,000	22,000	5,900
High	Airblast Applications	Citrus (CA and AZ)	6.0	36	180	360	1,800
Risk Estimates with 2000 Assessment Inhalation PoD (0.1 mg/kg/day) – LOC is an MOE =100							
Low	Groundboom Applications	Non-Crop Areas (Industrial Plant Sites, Road Medians, and Sod Farms), Turfgrass	0.25	1,100	5,100	10,000	8,100
Medium	Mixing/ Loading Liquids for Groundboom Application	Asparagus, Brussel Sprouts, Sugarbeet	1.0	400	2,000	4,000	1,100
High	Airblast Applications	Citrus (CA and AZ)	6.0	6	32	65	320

1. Single layer (long-sleeve shirt, long pants, shoes, socks), chemical resistant gloves
2. Double layer (single layer clothing with the addition of coverall), chemical resistant gloves

10.0 Incident Report

One component of the Agency's registration review program is consideration of human observational information including incident data, medical case reports, general medical information, biomonitoring data, and epidemiology studies. In conjunction with a human health risk assessment based on other data sources, such human incident and other human data can assist the Agency in better defining and characterizing the risk of pesticides/pesticide products. Based on the frequency and the effects noted in the Agency's earlier scoping or Tier I incident assessment (Hawkins M. and Cordova J., 10/15/2008), the Agency determined that chlorpyrifos human incident data are an important source of information to consider in its updated chlorpyrifos risk assessment.

HED has prepared a chlorpyrifos incident report review (S. Recore *et al*., 6/27/11, D388406, *Chlorpyrifos: Tier II Incident Report*). The review considers a variety of types and sources of human observational information including human incident data, medical data/case report information, and epidemiological information in an effort to inform the re-evaluation of chlorpyrifos in this phase of registration review. The human incident databases that were reviewed are:

- the OPP Incident Data System (IDS);
- the National Pesticide Information Center (NPIC);
- NIOSH's Sentinel Event Notification System for Occupational Risks (SENSOR);
- the California Pesticide Illness Surveillance Program Incident Data (CA PISP).

Together, these databases indicate that the number of incidents associated with chlorpyrifos declined post-2002, correlating well with the phase out/cancellation of the almost all chlorpyrifos residential products in December 2001. In addition, the Agency's findings are consistent with other incident cases investigations of American Association of Poison Control Centers **(**AAPCC) data which have reported a decrease in the number of chlorpyrifos incidents that is temporally associated with the phase out/cancellation of most residential chlorpyrifos products.

While the chlorpyrifos incidents are reported to have declined substantially (95%) among residential users from 2002 to 2010, it is unclear if occupational incidents have also decreased. Specifically, chlorpyrifos occupational incidents, reported in CA PISP and SENSOR databases, appear to be constant over time, despite risk mitigation implemented including reduced application rates and seasonal maximum limits, increased retreatment intervals, increased PPE and/or use of engineering controls which were required as well as increased reentry intervals (REIs) for a number of crops. However, a number of these incidents appear to be due to accidents and misuse. Overall, the NIOSH SENSOR database indicated that the largest number of incidents are exposures due to actual application of chlorpyrifos, but California PISP data suggests that drift of chlorpyrifos to adjacent fields appears to be the largest contributor to occupational exposure. OPP will continue to monitor these incidents and remain alert for any changes in trend or patterns.

In addition to the incident/poisoning data and medical case reports, epidemiological research can be an important source for human observational data and can potentially assist in identifying, characterizing, and (ideally) quantifying linkages between human exposures and resulting health effects. For chlorpyrifos, epidemiological data is available from both the Agricultural Health Study (AHS) and from a variety of university-based research groups. While the AHS investigations currently published were hypothesis-generating in nature, initial strength and consistency in the findings for lung cancer and colorectal cancer are notable, and warrant further follow-up and additional research. Preliminary associations with breast and prostate cancer are weak, but also warrant monitoring the literature for additional publications on this association. There is no compelling evidence of an association with other cancer sites including pancreatic cancer, melanoma, brain, esophageal, kidney, all lymphohematopoietic cancers combined and NHL, leukemia, and multiple myeloma (C. Christensen, 6/16/11, D388167).

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Appendix A. Toxicology Profile and Executive Summaries

A.1 Toxicology Data Requirements

The requirements (40 CFR 158.340) chlorpyrifos are in the table below. Use of the new guideline numbers does not imply that the new (1998) guideline protocols were used.

Study		Technical	
		Required	Satisfied
870.1100	Acute Oral Toxicity	yes	yes
870.1200	Acute Dermal Toxicity	yes	yes
870.1300	Acute Inhalation Toxicity	yes	yes
870.2400	Primary Eye Irritation	yes	yes
870.2500	Primary Dermal Irritation	yes	yes
870.2600	Dermal Sensitization	yes	yes
870.3100	Oral Sub-chronic (rodent)	yes	yes
870.3150	Oral Sub-chronic (non-rodent)	yes	yes
870.3200	21-Day Dermal	yes	yes+
870.3250	90-Day Dermal	CR	--
870.3465	90-Day Inhalation	CR	yes
870.3700a	Developmental Toxicity (rodent)	yes	yes
870.3700b	Developmental Toxicity (non-rodent)	yes	yes
870.3800	Reproduction	yes	yes
870.4100a	Chronic Toxicity (rodent)	yes	yes
870.4100b	Chronic Toxicity (non-rodent)	yes	yes
870.4200a	Oncogenicity (rat)	yes	yes
870.4200b	Oncogenicity (mouse)	yes	yes
870.4300	Chronic/Oncogenicity	yes	yes
870.5100	Mutagenicity—Gene Mutation - bacterial	yes	yes
870.5300	Mutagenicity—Gene Mutation - mammalian	yes	yes
870.5375	Mutagenicity—Structural Chromosomal Aberrations	yes	yes
870.5395	Mutagenicity—Other Genotoxic Effects (MN Assay)	yes	yes
870.6100a	Acute Delayed Neurotoxicity (hen)	yes	yes
870.6100b	90-Day Neurotoxicity (hen)	yes	yes
870.6200a	Acute Neurotoxicity Screening Battery (rat)	yes	yes
870.6200b	90-Day Neurotoxicity Screening Battery (rat)	yes	yes
870.6300	Developmental Neurotoxicity	yes	no, but upgradeable*
870.7485	General Metabolism	yes	yes
870.7600	Dermal Penetration	CR	yes
870.7800	Immunotoxicity	yes	yes
Special Studies	Comparative Cholinesterase Assay	yes	yes

CR: Conditionally Required, *Performed, But Guideline-Unacceptable Rating, Upgradeable if additional morphometric data is submitted

+Satisfied Guideline 82-2, but not 870.3200 since N<10/sex

A.2 Toxicity Profiles

Table A.2.1 Acute Toxicity Profile - Test Substance				
Guideline No.	**Study Type**	**MRID(s)**	**Results**	**Toxicity Category**
870.1100	Acute Oral LD50 - rat	44209101	223 mg/kg M&F	II
870.1200	Acute Dermal LD50 - rat Acute Dermal LD50 - rabbit	Accession No. 112115 44209102	202 mg/kg >5000 mg/kg	II, IV
870.1300	Acute Inhalation LC50; rat Supplementary	00146507 and Accession No. 257590	LC50 > 0.2 mg/L (200 mg/m3) (nominal concentration)	II
870.2400	Eye Irritation - rabbit	44209103	slight irritation resolved within 24 hours	IV
870.2500	Dermal Irritation - rabbit	44209104	mild irritant; (irritation resolved within 7 days)	IV
870.2600	Dermal Sensitization - guinea pig	44209105	non-sensitizing	NA

Table A.2.2 Chlorpyrifos Sub-chronic, Chronic and Special Studies Toxicity Profile			
Guideline No.	**Study Type**	**MRID# / Classification /Doses**	**Results**
870.3100	90-Day Oral Toxicity (Rat)	MRID #: 40436406 Acceptable/guideline 0, 0.025, 0.5, or 10 mg/kg/day (0, 0.5, 10 or 200 ppm)	95.5% a.i. chlorpyrifos NOAEL ChEI: none for plasma ChEI due to reductions in male plasma enzymes at 0.025 mg/kg/day LOAEL ChEI: 0.025 mg/kg/day (significant 22%↓ in plasma ChE activity that was dose-related) NOAEL (systemic): 0.5 mg/kg/day LOAEL (systemic): 10 mg/kg/day Effects: decreased weight gain and slight decreases in packed cell volume, red cells and hemoglobin Note: Female ChEI data is unreliable due to a possible reporting error. RBC and brain ChE activity were not measured.
870.3100	90-Day Oral Toxicity (Rat)	MRID #: 40952801 Acceptable/guideline 0, 0.1, 1, 5 or 15 mg/kg/day	95.7 - 98.5% a.i. chlorpyrifos NOAEL: 0.1 mg/kg/day (plasma and RBC ChEI) LOAEL: 1 mg/kg/day (significant plasma and RBC ChEI in both sexes) Effects: increased organ weights (brain and heart), and reduced weight gain at 15 mg/kg/day and increased adrenal gland vacuolation and significant brain ChEI in both sexes 5 and 15 mg/kg/day.
870.3150	Sub-chronic Oral (capsule) in Beagle Dogs	MRID #: 42172801 Acceptable/guideline 0, 0.01, 0.22, or 5 mg/kg/day	95.8% a.i. chlorpyrifos NOAEL: 0.01 mg/kg/day LOAEL: 0.22 mg/kg/day (significant 33-67% ↓ plasma and 24-46% ↓ RBC ChEI) Effects: Brain ChEI (46% ↓) occurred at 5 mg/kg/day. Comments: At 0.01 mg/kg/day, plasma ChEI noted in females (significant 20-24% at week 6, and non-significant 24% at week 12) and males (15% at week 13) that was not considered of sufficient magnitude and consistency to be biologically and toxicologically meaningful.

Table A.2.2 Chlorpyrifos Sub-chronic, Chronic and Special Studies Toxicity Profile			
Guideline No.	**Study Type**	**MRID# / Classification /Doses**	**Results**
870.3200	21-Day Dermal Toxicity Study in Rats	MRID # 40972801 Satisfies Guideline 82-2, but has less than 10 animals/sex for 870.3200 0, 0.1, 0.5, 1 or 5 mg/kg/day (21 day study) 0, 1, 10, 100 or 500 mg/kg/day (4-day dermal probe study)	100% pure chlorpyrifos NOAEL: 5 mg/kg/day (plasma and RBC ChEI) LOAEL: 10 mg/kg/day (45% plasma and 16% RBC ChEI following 4 days of exposure) NOAEL (systemic): 5 mg/kg/day LOAEL (systemic): Not Identified Effects: Slight erythema in 2/4 females at 1 and 10 mg/kg/day, respectively. 4-day Dermal Probe Study as well
870.3465	90-Day, Sub-chronic Inhalation in Rats (nose only)	MRID # 40013901 & 40166501 Acceptable/guideline 0, 5.2, 10.3 or 20.6 ppb (0, 72, 143 or 287 µg/m^3) (maximum dose equivalent to 0.044-0.082 mg/kg/day)	100% pure chlorpyrifos NOAEL: not identified (ChEI and systemic) LOAEL: not identified at highest attainable vapor concentration (>20.6 ppb or >0.082 mg/kg/day or >287 µg/m^3) (ChEI and systemic)
870.3465	90-Day, Sub-chronic Inhalation in Rats (nose only)	MRID # 40908401 Acceptable/guideline 0, 5, 10 or 20 ppb (0, 70, 143 or 287 µg/m^3) (equivalent to 0, 0.024, 0.048 or 0.097 mg/kg/day, respectively)	95% a.i. chlorpyrifos NOAEL: not identified (ChEI and systemic) LOAEL: not identified at highest attainable vapor concentration (>20 ppb or 0.097 mg/kg/day) (ChEI and systemic)
870.3700a	Developmental Study in CD rats (gavage)	MRID# 40436407 Acceptable/guideline 0, 0.5, 2.5 or 15 mg/kg/day (gestation day 6-15)	96.1% a.i. chlorpyrifos Maternal NOAEL: none observed for plasma ChEI; 2.5 mg/kg/day for systemic Maternal LOAEL: 0.5 mg/kg/day (decreased plasma ChEI); 15 mg/kg/day (systemic) based on decreased food consumption (only the first few days of dosing) and body weight during dosing. Developmental NOAEL: 2.5 mg/kg/day Developmental LOAEL: 15 mg/kg/day (HDT) based on an increase in post-implantation loss. Comments: RBC and brain ChE were not measured.

Table A.2.2 Chlorpyrifos Sub-chronic, Chronic and Special Studies Toxicity Profile			
Guideline No.	**Study Type**	**MRID# / Classification /Doses**	**Results**
870.3700a	Developmental Study in F344 rats (gavage)	MRID# 00130400 Acceptable/guideline 0, 0.1, 3, or 15 mg/kg/day (gestation day 6-15)	96.6% a.i. chlorpyrifos Maternal NOAEL: 0.1 mg/kg/day (plasma and RBC ChEI) Maternal LOAEL: 3 mg/kg/day (90.3% plasma and 74.3% RBC ChEI) Developmental NOAEL: 15 mg/kg/day (HDT) Developmental LOAEL: Not Identified
870.3700a	Developmental Study in CF-1 Mice (gavage)	MRID# 00095268 Unacceptable/Non-guideline 0, 0.1, 1, 10, or 25 mg/kg/day (gestation day 6-15)	96.8% a.i. chlorpyrifos Maternal NOAEL: 0.1 mg/kg/day (plasma and RBC ChEI); 10 mg/kg/day (systemic toxicity) Maternal LOAEL: 1 mg/kg/day (plasma and RBC ChEI); 25 mg/kg/day (systemic toxicity) based on decreased body weight, food and water consumption, and increased mortality. Developmental NOAEL: 1 mg/kg/day (plasma and RBC ChEI); 10 mg/kg/day for systemic toxicity Developmental LOAEL: 10 mg/kg/day (plasma and RBC ChEI); 25 mg/kg/day (systemic toxicity) based on minor skull variations, delayed ossification of skull bones and sternebrae and reduced fetal body length. Comments: Brain ChE not measured.
870.3700b	Developmental Study in New Zealand rabbits (gavage)	MRID# 40436408 Acceptable/guideline 0, 1, 9, 81, or 140 mg/kg/day (gestation day 7-19)	96.1% a.i. chlorpyrifos Maternal NOAEL: none observed for plasma ChEI; 81 for systemic toxicity Maternal LOAEL: 1 mg/kg/day (plasma ChEI); 140 for systemic toxicity based on reduced food consumption, body weight loss, and apparent post-implantation loss. Developmental NOAEL (systemic): 81 mg/kg/day Developmental LOAEL (systemic): 140 mg/kg/day based on slightly decreased fetal weights and crown-rump lengths, and an increased incidence of unossified xiphisternum and/or 5th sternebra.

Table A.2.2 Chlorpyrifos Sub-chronic, Chronic and Special Studies Toxicity Profile			
Guideline No.	**Study Type**	**MRID# / Classification /Doses**	**Results**
870.3800	2-Generation Reproduction Toxicity in SD Rats	MRID# 41930301 Acceptable/guideline 0, 0.1, 1, or 5 for 10 mg/kg/day (F0) or 12 (F1) weeks prior to mating, through lactation and weaning	97.8-98.5% a.i. chlorpyrifos Parental NOAEL: 0.1 mg/kg/day Parental LOAEL: 1 mg/kg/day (significant 43-59% plasma, and 65-69% RBC ChEI at 1 mg/kg/day; and 48-49% brain ChEI and histological lesions of the adrenal gland at 5 mg/kg/day). Reproductive NOAEL: 1 mg/kg/day Reproductive LOAEL: 5 mg/kg/day (HDT) based on reduced pup weight and increased pup mortality in F1 generation only.
870.3800	3-Generation Reproduction Toxicity in SD Rats	MRID # 00029064, 00064934 Acceptable/guideline 0, 0.03, 0.1,or 0.3 mg/kg/day for first generation, and 0.1, 0.3 or 1 mg/kg/day for second and third generation	Parental NOAEL: 0.1 mg/kg/day Parental LOAEL: 0.3 mg/kg/day (plasma and RBC ChEI) Reproductive NOAEL: 1 mg/kg/day (HDT) Reproductive LOAEL: Not Identified
870.3800	Reproduction Study in Rats	MRID# 00130401 Acceptable in combination with studies 00029064 & 00064934 0, 0.5, 0.8, 1.2 mg/kg/day in Sprague-Dawley Rats	NOAEL Neonatal Survival: 1.2 mg/kg/day (Primary purpose of the study) NOAEL Reproduction: 1.2 mg/kg/day NOAEL General Toxicity: 0.8 mg/kg/day LOAEL General Toxicity: 1.2 mg/kg/day based on decreased weight gain in males
870.4100a	Chronic feeding study in CD-1 mice (2 yrs)	MRID # 00054352 & 00142902 (Accession No. 242059) Acceptable/guideline 0, 0.5, 5 or 15 ppm (highest dose tested is 2.25 mg/kg/day)	99.6% a.i. chlorpyrifos LOAEL: 2.25 mg/kg/day (90%↓plasma, and 50%↓ RBC ChE activity relative to controls after 1 week) NOAEL(systemic) = 2.25 mg/kg/day LOAEL (systemic): Not Determined Effects: no systemic effects observed at highest dose tested (HDT). No treatment-related tumors. ChE only measured at 15 ppm (2.25 mg/kg/day) after 1 and 4 weeks.

Table A.2.2 Chlorpyrifos Sub-chronic, Chronic and Special Studies Toxicity Profile			
Guideline No.	**Study Type**	**MRID# / Classification /Doses**	**Results**
870.4100b	Chronic feeding study in beagle dogs (2 yrs)	MRID # 00064933 & 00146519 Acceptable/guideline 0, 0.01, 0.03, 0.1, 1 or 3 mg/kg/day	97.2-98.8% a.i. chlorpyrifos NOAEL: 0.01, 0.03, & 1 mg/kg/day for plasma, RBC and brain ChEI, respectively LOAEL (plasma ChEI): 0.03 mg/kg/day (mostly significant mean of 23-29% ↓ at 1 year and 10-24% ↓ at 2 years) LOAEL (RBC ChEI): cannot be established due to data quality issues LOAEL (brain ChEI): 3 mg/kg/day (19.4-20.8% ↓ at 2 yr) NOAEL (systemic): 1 mg/kg/day LOAEL (systemic): 3 mg/kg/day Effects: increased absolute and relative liver weights that could be an adaptive response
870.4200a	Carcinogenicity /chronic feeding study in F344 rats (2 yrs)	MRID # 42172802 Acceptable/guideline Males: 0, 0.0132, 0.33 or 6.99 mg/kg/day Females: 0, 0.0146, 0.365 or 7.78 mg/kg/day (0, 0.2, 5 or 100 ppm)	96.1% a.i. chlorpyrifos NOAEL:0.0132 mg/kg/day LOAEL: 0.33 mg/kg/day (significant 15-51% plasma ChEI in both sexes, 19-31% RBC ChEI at 104 weeks vs. controls and 11-17% RBC ChEI vs. vehicle controls) NOAEL (systemic):0.33 mg/kg/day LOAEL (systemic): 6.99 mg/kg/day Effects: decreased body weights in males and females, and cataracts, and diffuse retinal atrophy in females. No evidence of carcinogenicity.

Table A.2.2 Chlorpyrifos Sub-chronic, Chronic and Special Studies Toxicity Profile			
Guideline No.	**Study Type**	**MRID# / Classification /Doses**	**Results**
870.4200a	Carcinogenicity /chronic feeding study in F344 rats (2 yrs)	MRID # 40952802 Acceptable/guideline 0, 0.05, 0.1, 1 or 10 mg/kg/day	Lorsban 98.5% pure NOAEL: 0.1 mg/kg/day (plasma and brain ChEI) LOAEL: 1 mg/kg/day (significant 39-86% plasma, 14-34% RBC and 5-9% brain ChEI) NOAEL (systemic): 1 mg/kg/day LOAEL (systemic): 10 mg/kg/day Effects: decreased body weight gain, red blood cells, hemoglobin, cholesterol, protein, and globulin, and increased platelets and specific gravity, increased adrenal gland weight, and fatty vacuolation of the zona fasciculata. No evidence of carcinogenicity.
870.4200b	Carcinogenicity/ chronic feeding study in CD-1 mice (78 weeks)	MRID # 42534201 Acceptable/guideline Males: 0, 0.89, 8.84, 45.2 mg/kg/day Females: 0, 0.938, 9.79, or 48.1 mg/kg/day (0, 5, 50 or 250 ppm)	95.5% a.i. chlorpyrifos NOAEL: none for ChEI LOAEL: 0.89 males; 0.938 females mg/kg/day (significant 45-51% plasma ChEI in both sexes) NOAEL (systemic): 8.84 males, 9.79 females mg/kg/day (50 ppm) LOAEL (systemic): 48.1 females, 45.2 males mg/kg/day (HDT; 250 ppm) Effects: decreased body weight gain and food consumption in males, decreased water consumption in females, increased incidences of keratitis and hepatocyte fatty vacuolation, and increased incidence of gross clinical findings (ocular opacity and hair loss) in both sexes. Brain cholinesterase was inhibited at the high dose in both sexes. No evidence of carcinogenicity. Brain ChEI at high dose. Note: The validity of the RBC ChE assay is questionable.

Table A.2.2 Chlorpyrifos Sub-chronic, Chronic and Special Studies Toxicity Profile			
Guideline No.	**Study Type**	**MRID# / Classification /Doses**	**Results**
870.5100	Gene Mutation Bacterial Cell (Ames Reversion)	MRID# 00157058 and 40436411 Acceptable/guideline Tested in Salmonella strains TA 98, TA 100, TA 1535, TA 1537 and TA 1538 in the presence and absence of S-9 at concentrations of 30, 100, 300, 1000, 3000 and 10000 µg/plate	Negative for reverse mutations Positive controls caused appropriate mutagenic responses.
870.5300	Gene Mutation Mammalian Cell (CHO Cells/HGPRT)	MRID# 00152683 and 40436410 Acceptable/guideline Tested for gene mutation potential at 0, 10, 20, 25, 30, 40 & 50 µM in mammalian cells	Negative for reverse mutations Cytotoxic at 10 µM and above without metabolic activation and no toxicity with activation. Precipitate formed at 30 µM and higher concentrations with or without activation.
870.5375	In vitro Cytogenetics	MRID# 40436409, 44533401 Acceptable/guideline Concentrations assayed were as follows with non-activation in the 10 hour assay at 1.56, 3.12, 5.2, 10.4, 15.6, 31.2, 52, 104 & 156 µg/ml and in the 19-20 hour assay at 0.975, 1.47, 2.93, 4.89, 9.75, 14.7, 29.3, 48.9, 97.5 & 147 µg/ml. Concentrations tested with activation in the two 10 hour assays were 1, 1.5, 3, 5, 10, 15, 30, 50 & 100 µg/ml and 2.95, 4.95, 9.85, 14.8, 29.6, 49.4, 98.5 & 296 µg/ml, plus concentrations for the 19-20 hour assay were 9.75, 14.7, 29.3, 48.9, 97.5, 147 & 293 µg/ml.	Negative for chromosome aberrations Cytotoxicity was shown in both non-activated as well as in activated assays. Positive controls mitomycin C (for non-activation) and cyclophosphamide (for activation) caused the appropriate mutagenic responses.

Table A.2.2 Chlorpyrifos Sub-chronic, Chronic and Special Studies Toxicity Profile			
Guideline No.	**Study Type**	**MRID# / Classification /Doses**	**Results**
870.5395	Micronucleus Assay in Mammalian Erythrocytes	MRID# 00152684 Acceptable/guideline Tested at levels of 0, 7, 22, 70 mg/kg by gavage in corn oil in the mouse	Not clastogenic
870.5500	DNA Repair Assay in Bacteria	Accession# 256040 Acceptable/guideline	Increased damage to DNA was detected
870.5550	Unscheduled DNA Synthesis in Rat Hepatocytes	MRID# 00157057 Acceptable/guideline Tested with concentrations from 10E-06 M to 10E-04 M in isolated rat hepatocytes	Negative for induction of UDS The high dose was cytotoxic and also formed a precipitate.
870.5575	Mitotic Gene Conversion in Yeast	Accession# 256040 Acceptable/guideline	Increased recombination frequency detected
870.6100a	Acute Delayed Neurotoxicity Study in Hens	MRID# 00097144 and 40510601 Acceptable/guideline 0, 50, 100 or 110 mg/kg	96.8% a.i. chlorpyrifos NOAEL: 110 mg/kg (HDT) LOAEL: Not Determined Not neurotoxic
870.6200a	Acute Neurotoxicity Study in Rats	MRID 42669101 and 42943101 Acceptable/guideline 0, 10, 50 or 100 mg/kg	98.2% a.i. chlorpyrifos NOAEL (systemic): 10 mg/kg LOAEL (systemic): 50 mg/kg Effects: Decreased body weight, and motor activity and increased incidence of adverse clinical signs

Table A.2.2 Chlorpyrifos Sub-chronic, Chronic and Special Studies Toxicity Profile			
Guideline No.	**Study Type**	**MRID# / Classification /Doses**	**Results**
870.6200b	13-Week Rat Neurotoxicity Study in Rats	MRID 42929801 Acceptable/guideline 0, 0.1, 1, 5, or 15 mg/kg/day	98.2% a.i. chlorpyrifos NOAEL (systemic): ≥15 mg/kg/day LOAEL (systemic): none established Effects: Decreased motor activity and an increased incidence of urine incontinence in females. Note: This study did not measure cholinesterase activity.
870.6300	Developmental Neurotoxicity in Rats	MRID: 44556901 Guideline-Unacceptable, But Upgradeable 0, 0.3, 1, or 5 mg/kg/day (gestation day 6 through lactation day 11)	99.8% a.i. chlorpyrifos Maternal NOAEL: none observed for plasma or RBC ChEI Maternal LOAEL: ≤0.3 mg/kg/day (43%↓ plasma and 41%↓% RBC ChE activity relative to controls) Note: Submission of further morphometric data may upgrade the study.
	Cholinesterase and Metabolite Determination Study in Rats (Companion Study of the Developmental Neurotoxicity Study)	MRID# 44648101 Acceptable/Non-Guideline 0, 0.3, 1, or 5 mg/kg/day (gestation day 6 through lactation day 11)	99.8% a.i. chlorpyrifos Maternal Effects: Dams in the 0.3 mg/kg/day group exhibited a 33%↓ plasma and 26↓% RBC ChE activity relative to controls Developmental Effects: Pups in the 5 mg/kg/day group exhibited an 85%↓ plasma, 92↓% RBC, 82%↓ heart and 60%↓ brain ChE activity relative to controls Note: This is a pharmacokinetic study, and therefore, NOAELs and LOAELs were not identified.
870.7485	Acute Pharmacokinetic Study in Rats	MRID 44648102 Acceptable/Non-Guideline 0.5, 1, 5, 10, 50, 100 mg/kg	89.4-99.8% a.i. chlorpyrifos NOAEL: 0.5 mg/kg LOAEL: 1 mg/kg (28-40% plasma ChEI at the peak time of inhibition, 3-6 hours post exposure) Other: significant brain ChEI at doses ≥10 mg/kg Note: red blood cell ChE measurements were not collected.

Table A.2.2 Chlorpyrifos Sub-chronic, Chronic and Special Studies Toxicity Profile			
Guideline No.	**Study Type**	**MRID# / Classification /Doses**	**Results**
870.7485	Metabolism and Pharmacokinetics In Fischer 344 Rats	MRID# 40458901 Acceptable/guideline 0.5 or 25 mg/kg of ^{14}C labeled chlorpyrifos or 15 daily doses of 0.5 mg/kg unlabeled chlorpyrifos followed by one dose of 0.5 mg/kg of ^{14}C labeled chlorpyrifos.	During 72 hours, more than 84% of the radioactivity was recovered in the urine, about 5% was found in the feces and less than 0.2% was found in the tissues and carcass. The metabolism of chlorpyrifos was extensive, and no unchanged parent compound was found in the urine. The major urinary metabolites were TCP, as well as glucuronide and sulfate conjugates of TCP.
870.7485	Metabolism and Pharmacokinetics In Fischer 344 Rats	MRID# 44648102 Acceptable, Non-guideline 0.5, 1, 5, 10, 50, or 100 mg/kg and followed vs time Four male rats were given a single gavage dose of labeled chlorpyrifos at a concentration of 5 or 100 mg/kg and were sacrificed three hours later.	Peak chlorpyrifos blood concentrations occurred within three hours of treatment. Plasma ChE activity decreased in a time- and dose-dependent manner. The plasma ChE activities of rats treated with 0.5, 1, 5 or 10 mg/kg were maximally decreased 3-6 hours after treatment, with both the decrease and recovery of activity being dose-dependent. In the 1 mg/kg dose group, plasma ChE activity was significantly inhibited approximately 28% and 40% relative to controls at 3 and 6 hours post exposure, respectively. By 12 hours post-exposure, plasma ChE activity was still significantly inhibited about 16% for the 1 mg/kg group. The decrease in plasma ChE activity of rats treated with 50 or 100 mg/kg began within 10 minutes of treatment. By 12 hours after treatment, plasma ChE activity in both groups were approximately 11% of the control group and had not shown signs of recovery. Brain cholinesterase activity was not affected as dramatically by test material treatment as plasma activity with only the 10, 50, and 100 mg/kg dose groups showing significant effects. The brain cholinesterase activity of rats treated with 10 mg/kg test material began to decline within three hours of treatment and was significantly decreased by six hours after treatment. The brain cholinesterase activity in the 50 or 100 mg/kg dose groups decreased significantly within one hour of treatments; and by 12 hours, it was approximately 30% and 20%, respectively, of control. In none of the affected groups did brain cholinesterase show signs of recovery.

Table A.2.2 Chlorpyrifos Sub-chronic, Chronic and Special Studies Toxicity Profile			
Guideline No.	**Study Type**	**MRID# / Classification /Doses**	**Results**
870.7600	Dermal Penetration (Human)	Accession No. 249203 Single doses of 0.5 mg/kg (N=1) and 5.0 mg/kg (N=5) to male humans	Based on the urinary excretion of the 3,5,6-TCP metabolite, the minimum absorption was approximately 1-3% dermally. The proportion of the administered dose metabolized to this pyridinol is unknown, these estimates are considered minimum values (i.e. absorption could be higher).
870.7800	Immunotoxicity in Female Crl:CD(SD) Rats	MRID 48139304 Acceptable/guideline 0, 0.416, 2.13, or 10.7 mg/kg/day	NOAEL is 10 mg/kg/day LOAEL not established
Special Study	Special Acute Neurotoxic Esterase (NTE) Rat Study	MRID 44273901 Acceptable/Non-guideline 0, 1, 5, 10, 50 or 100 mg/kg	98.1% a.i. chlorpyrifos NOAEL: 1 mg/kg [plasma ChE, and RBC and heart acetyl cholinesterase (AChE)] LOAEL: 5 mg/kg (45% plasma ChEI; 17% RBC AChEI; and 19% heart AChEI). Effects: NTE was not inhibited at any dose. Note: cholinesterase measurements were made 24 hours post exposure.
Special Study	Cognitive Rat Study	MRID 44020901 Acceptable/Non-Guideline 0, 1, 3, or 10 mg/kg/day for 5 days/week for 4 weeks	98.1% a.i. chlorpyrifos NOAEL: none observed (plasma and RBC ChE), LOAEL: 1 mg/kg/day (68% plasma ChEI; 56% RBC ChEI and 8% brain ChEI). NOAEL (systemic): 1 mg/kg/day (miosis) LOAEL (systemic): 3 mg/kg/day (miosis)

Table A.2.2 Chlorpyrifos Sub-chronic, Chronic and Special Studies Toxicity Profile			
Guideline No.	**Study Type**	**MRID# / Classification /Doses**	**Results**
Special Study	Comparative Cholinesterase Assay	MRID 48139301 Acceptable/Non-Guideline	Repeat Dosing Data Chlorpyrifos (CPY) & Oxon (CPO) NOAEL/LOAEL in mg/kg/day (% Inhibition) Plasma ChE: Pups & Adult CPY 0.1/0.5 (46%) & 0.1/0.5 (46%) CPO 0.01/0.5 (62%) & 0.01/0.5 (76%) RBC ChE: Pups & Adult CPY 0.1/0.5 (18%) & 0.1/0.5 (20%) CPO 0.01/0.5 (84%) & 0.01/0.5 (87%) Brain ChE: Pups & Adult CPY 0.5/1 (19%) & 0.5/1 (9%) CPO Not inhibited & Not inhibited
Special Study	Acute Inhalation Study	MRID 48139303 Acceptable/Non-Guideline	NOAEL Not Identified LOAEL 3.7 mg/m^3 based on lung cholinesterase activity

A.3 Hazard Identification and Endpoint Selection

A.3.1 Acute Population Adjusted Dose (aPAD) - Females age 13-49

No endpoint selected for this category.

A.3.2 Acute Population Adjusted Dose (aPAD) - General Population

Study Selected: Comparative Cholinesterase Assay (CCA)
MRID No.: 48139301
Executive Summary: See Appendix A.4.9
Dose and Endpoint for Risk Assessment: $BMDL_{10}$=0.36 mg/kg
Comments about Study/Endpoint/Uncertainty Factors: The CCA study is currently thought to be the most appropriate endpoint for chlorpyrifos. The UF_A=10 and the UF_H=10, with a proposed FQPASF =1. The acute PAD=0.0036 mg/kg/day.

A.3.3 Chronic PAD

Study Selected: DNT Gavage Study in Pregnant Rats
MRID No.: 44648101 and 44556901
Executive Summary: See Appendix A.4.7, Guideline 870.6300
Dose and Endpoint for Risk Assessment: $BMDL_{10}$=0.03 mg/kg/day
Comments about Study/Endpoint/Uncertainty Factors: The ChE data is currently thought to be the most appropriate endpoint for chlorpyrifos. The UF_A=10 and the UF_H=10, with a proposed FQPA SF=1. The chronic PAD=0.0003 mg/kg/day.

A.3.4 Incidental Oral Exposure (Short- and Intermediate-Term)

Short Term Exposure

Study Selected: Repeat Oral CCA Study in Rat
MRID No.: 48139301
Executive Summary: See Appendix A.4.9 Special Studies
Dose and Endpoint for Risk Assessment: $BMDL_{10}$=0.1 mg/kg/day
Comments about Study/Endpoint/Uncertainty Factors: The CCA study is currently thought to be the most appropriate endpoint for chlorpyrifos. The UF_A=10 and the UF_H=10, with a proposed FQPA SF=1.

Intermediate Term Exposure
See Chronic Dietary Endpoint

A.3.5 Dermal Exposure (Short-, Intermediate- and Long-Term)

Study Selected: 21-Day Dermal Study
MRID No.: 40972801
Executive Summary: See Appendix A.4.1, Guideline 870.3200

Dose and Endpoint for Risk Assessment: NOAEL = 5 mg/kg/day based on plasma and RBC ChE inhibition seen at LOAEL = 10 mg/kg/day.
Comments about Study/Endpoint/Uncertainty Factors: A repeated dose dermal study is the most appropriate study for this exposure and ChE inhibition is the most appropriate assay. The UF_A=10, the UF_H=10, the proposed FQPA SF =1 (residential exposures).

A.3.6 Inhalation Exposure (Acute, Short- and, Intermediate-Term)

Acute Exposure

Study Selected: Acute Inhalation Study
MRID No.: 48139303
Executive Summary: See Appendix A.4.9, Special Study
Dose and Endpoint for Risk Assessment: LOAEL = 3.7 mg/m^3 and the HEC = 0.62 mg/m3 (RfC=0.00021 mg/m^3) based on ChE inhibition. A NOAEL was not identified.
Comments about Study/Endpoint/Uncertainty Factors: This study is appropriate since it is the correct exposure of inhalation and ChE activity is appropriate as an endpoint for chlorpyrifos. For residential: The UF_A=3, UF_H=10, FQPA UF_{DB} =10 (extrapolation of LOAEL to NOAEL).

Short and Intermediate Term Exposure

Study Selected: 90-Day Inhalation Studies
MRID No.: 40908401, 40013901, 40166501, 44556901
Executive Summary: See Appendix A.4.1, Guideline 870.3465
Dose and Endpoint for Risk Assessment: NOAEL (calculated from an HEC) = 0.56 mg/kg/day (for occupational) and HEC = 0.0057 mg/m3) based on ChE inhibition seen at LOAEL = 0.3 mg/kg/day in the DNT study.
Comments about Study/Endpoint/Uncertainty Factors: This study is appropriate since it is the correct exposure of inhalation and ChE activity is appropriate as an endpoint for chlorpyrifos. The HEC=0.0057 mg/m^3. For residential: UF_A=3, UF_H=10, FQPA SF=1. For occupational: UF_A=3, UF_H=10.

A.4 Executive Summaries

A.4.1 Sub-chronic Toxicity

870.3100 90-Day Oral Toxicity – Rat

In a sub-chronic oral toxicity study in rats (MRID 40436406), chlorpyrifos (95.5% a.i.) was fed to 20 rats/sex/dose at dose levels of 0, 0.5, 10 or 200 ppm (equivalent to 0, 0.025, 0.5 or 10 mg/kg/day) for 13 weeks.

There were no treatment related effects on mortality, clinical signs, histopathology or organ weights. A significant decrease in body weight gain was observed in high dose males during the first half of the study, and in high dose females during the first three weeks. However, body weight in exposed animals was similar to controls by week 13. Food consumption in the high-

dose animals was also significantly increased during the time of increase body weight gain. Hematological effects were observed in both high-dose males and females, characterized by significantly reduced packed cell volume (PCV), hemoglobin (HB) and erythrocyte (RBC) group means relative to controls, which is suggestive of anemia. However, these parameters were within the normal range. Urinalysis revealed that males in the high dose group had a significantly reduced urine volume, increased urine pH, a higher specific gravity and a higher protein grading, which appear to be treatment-related.

No biologically or significant or treatment-related differences were noted for clinical chemistry parameters, with the exception of cholinesterase (ChE) inhibition. Significant and dose-related plasma ChE inhibition of 22, 37 and 72% was observed in the 0.5, 10 and 200 ppm male groups, respectively. In females, plasma cholinesterase was also significantly inhibited at 91 and 57% for the 10 and 200 ppm groups, respectively, but was not inhibited in the low dose group (10% increase). However, the registrant acknowledged the possibility that the cholinesterase data for the 10 and 200 ppm female groups were accidently switched. Red blood cell and brain cholinesterase activity were not evaluated in this study.

The LOAEL for plasma cholinesterase inhibition is 0.5 ppm (0.025 mg/kg/day) for males, which is the lowest dose tested. No NOAEL was observed for cholinesterase inhibition. The systemic NOAEL and LOAEL are 10 and 200 ppm, respectively (0.5 and 10 mg/kg/day, respectively) based on decreased body weight gains and possible anemia. The study is classified as acceptable/guideline.

Chlorpyrifos was administered (0.1, 1, 5, and 15 mg/kg/day) in the diet for 90 days to CDF Fischer 344 rats (MRID 40952801). Body weight and body-weight gain were decreased in the high dose males (15 mg/kg) at the beginning (first 4 weeks) and near the end (day 70 on) of the study. Plasma and RBC cholinesterase activities were decreased in both sexes at the interim time point at 1, 5, and 15 mg/kg (dose-related) and in females at the 0.1 mg/kg dose level. At termination, brain cholinesterase was decreased (dose-related) at the 5 and 15 mg/kg dose levels in both sexes; plasma cholinesterase activity was decreased at 1, 5 and 15 mg/kg in both sexes; and erythrocyte cholinesterase activity was decreased in both sexes at 5 and 15 mg/kg and in females also at 1 mg/kg. The only other treatment-related effect was increased vacuolation in the adrenal gland in males of the 5 and 15 mg/kg dose groups.

The NOAEL can be set at 0.1 mg/kg, the LOAEL at 1 mg/kg, based on decreased plasma and RBC cholinesterase activities. The study is classified as acceptable/guideline.

870.3150 90-Day Oral Toxicity – Dog

In a sub-chronic oral toxicity study in dogs (MRID 42172801), chlorpyrifos (95.8% a.i.) was administered by gelatin capsule to 4 beagle dogs/sex/dose at dose levels of 0, 0.01, 0.22, or 5 mg/kg/day each day for 13 weeks.

There were no treatment related effects on mortality, clinical signs, body weight, food consumption, ophthalmological examination, urinalysis, or organ weights. Although some statistically significant differences were noted in some hematological parameters, these findings were not considered biologically significant, or treatment related. No biologically significant

differences were noted for clinical chemistry parameters, with the exception of cholinesterase (ChE) inhibition. Significant and dose-related plasma and red blood cell ChE inhibition were observed in both sexes throughout the study. Plasma ChE was significantly inhibited in males (33-63%) and females (42-67%) exposed to 0.22 mg/kg/day and in males (69-85%) and females (64-87%) exposed to 5 mg/kg/day. Red blood cell ChE was also significantly inhibited in males (32-46%) and females (24-38%) exposed to 0.22 mg/kg/day during weeks 6 and 12 and in males (38-85%) and females (29-86%) exposed to 5 mg/kg/day during weeks 1, 6 and 12. Brain ChE activity was significantly reduced 46% at 5 mg/kg/day in both males and females. Although possible treatment-related gross and microscopic pathology changes were observed in the high dose animals, these findings were not observed in the 2-year dog study, and only occurred in one male and one female. These include a thickened muscular wall of the duodenum and an area of papillomatous hyperplasia (pyloric).

The NOAEL and LOAEL for plasma and red blood cell cholinesterase inhibition are 0.01 and 0.22 mg/kg/day, respectively. The study is classified as guideline/acceptable.

870.3200 21/28-Day Dermal Toxicity – Rat

In a 21-day dermal toxicity study (MRID 40972801), 5 Fischer 344 rats/sex/dose were dermally exposed to 0, 0.1, 0.5, 1 or 5 mg/kg/day chlorpyrifos (100% a.i.) in corn oil on a 12 cm^2 area of the back once per day, 6 hours/application, 5 days/week for a total of 15 applications in 21 days. In a 4-day dermal probe study used to select the doses, 4 female Fischer 344 rats/dose were similarly treated via dermal application at dose levels of 0, 1, 10, 100 or 500 mg/kg/day chlorpyrifos in corn oil for four consecutive days.

In the 21-day study, there were no signs of treatment-related systemic or dermal toxicity at doses up to 5 mg/kg/day, including effects on cholinesterase inhibition, body weight, food consumption, ophthalmological examination, hematology, or clinical chemistry. In the 4-day probe study, 2 of 4 females in the 1 and 10 mg/kg/day groups developed slight erythema. Dose-related plasma (45, 92 and 98%↓) and red blood cell (16, 49 and 75%↓) cholinesterase inhibition were observed in the 10, 100 and 500 mg/kg/day groups. However, statistical analyses were not conducted. The cholinesterase activities of the 1 mg/kg/day females were slightly decreased, but within the historical control range. No other treatment-related effects were noted in the dermal probe study.

The NOAEL and LOAEL for plasma and red blood cell cholinesterase inhibition are 5 and 10 mg/kg/day, respectively, based on the results of both the 21-day and 4-day dermal probe studies. Satisfies the guideline requirement (82-2), but not guideline 870.3200, which requires 10 animals/sex/dose for dermal toxicity testing.

870.3465 90-Day Inhalation – Rat

In a sub-chronic nose-only inhalation study (MRID 40908401), Fischer 344 rats (10/ sex/ concentration) were exposed nose only to Chlorpyrifos (95% a.i.) at vapor concentrations of 0, 5, 10, or 20.6 ppb (0, 72, 143 or 287 $\mu g/m^3$, respectively) 6 hours/day, 5 days/week for 13 weeks. These concentrations resulted in estimated maximum exposures of 0, 0.024, 0.048 and 0.097

mg/kg/day, respectively based on the EPA default ventilation rate of 0.00715 m^3/hr for rats (average of males and females), and average study specific body weights of 0.189 and 0.127 kg for male and female controls, respectively. The study author stated that the saturation or near saturation level was 20 ppb.

There were no treatment-related effects on mortality, body weight, clinical signs, ophthalmoscopy, hematology, gross pathology or histopathology. In females, food consumption was slightly depressed throughout the study in all dose groups without correlation to the dose level, although this observation was not considered of toxicological significance due to only slight decreases in corresponding body weights. There were some sporadic differences in clinical chemistry parameters, although these were not considered treatment-related due to a lack of dose-response and inconsistency between interim and terminal values. Sporadic differences in organ weights also were not considered treatment-related and appeared to be attributed to the increase mean body weights.

Significant plasma cholinesterase (ChE) inhibition was observed in the high dose males (23%) and females (25%) at the terminal sacrifice. Significant plasma ChE inhibition was also noted in females of the 5 and 10 ppb groups (26 and 40%, respectively), although a dose-response relationship was not apparent. Interim (8 week) measurements were similar or slightly greater than controls. Red blood cell (RBC) (interim and terminal) and brain (terminal) ChE activities were not significantly inhibited at any dose level. It should be noted that the chlorpyrifos concentrations in the exposure chambers at 13 weeks were approximately 12, 16 and 24 ppb, which exceeds the 5, 10 and 20 ppb average exposure levels and this may partially explain the terminal results, while the 8 week concentrations were closer to the average levels. The plasma ChE inhibition was not considered of toxicological significance because of the minimal inhibition (23-25%) at the high dose, lack of dose-response, and an absence of inhibition in the 8 week interval.

No LOAEL was identified in this study. Therefore, the NOAEL for systemic effects and plasma cholinesterase inhibition exceeds 20 ppb or 0.097 mg/kg/day. This study is classified as acceptable/guideline.

In a sub-chronic, nose-only inhalation study (MRID 40013901 & 40166501), Fischer 344 rats (10/sex/concentration) were exposed nose only to Chlorpyrifos at vapor concentrations of 0, 5.2, 10.3, or 20.6 ppb (0, 72, 143 or 287 $\mu g/m^3$, respectively) 6 hours/day, 5 days/week for 13 weeks. Cholinesterase activity was measured at study termination. The maximum dose to rats in the 20.6 ppb group was estimated to be 0.044-0.082 mg/kg/day based on average study specific body weights of 0.15 and 0.282 kg for female and male control animals, respectively and the EPA default rat ventilation rate of 0.00715 m^3/hr (average for males and females).

There were no treatment-related effects on body weight, clinical signs, urinalysis, hematology, clinical chemistry, organ weights, gross pathologic or histopathologic evaluations, or plasma, red blood cell or brain cholinesterase activities. Although female rats of all treatment groups had a slight (<4%) but significant decrease in red blood cell count, and males of all treatment groups had slightly elevated (approximately 13%) serum urea nitrogen, these observations were not

considered treatment-related due to a lack of dose-response, and all values were within the historical control range.

No LOAEL was identified in this study. Therefore, the NOAEL for systemic toxicity and cholinesterase inhibition exceeds 20 ppb or 0.082 mg/kg/day. The studies are classified as acceptable/guideline.

A.4.2 Prenatal Developmental Toxicity

870.3700a Prenatal Developmental Toxicity Study – Rat

Chlorpyrifos was dosed via gavage at 0, 0.5, 2.5 and 15 mg/kg/day in CD rats during gestation day 6-15 (MRID 40436407).

Based on ChE inhibition, the maternal NOAEL is < 0.5 mg/kg/day (LDT) with the maternal systemic toxicity NOAEL =15 mg/kg/day. The maternal systemic toxicity LOAEL =15 mg/kg/day (decrease in food consumption only first few days of dosing) and decrease in body weight gain during dosing. The developmental toxicity NOAEL = 2.5 mg/kg with the LOAEL =15 mg/kg/day (increase in post implantation loss). This study is classified as acceptable/guideline.

In a developmental toxicity study (MRID 00130400) Chlorpyrifos, 96.6% a.i., was administered to Fischer 344 rats by gavage at dose levels of 0 (corn oil vehicle only), 0.1, 3.0, or 15 mg/kg/day from days 6 through 15 of gestation. There were 31 rats each in the control and the 0.1 mg/kg/day (LDT) groups and 32 in the 3.0 mg/kg/day (MDT) group and 33 in the 15 mg/kg/day (HDT) group.

Maternal toxicity - There were no deaths in any group. Food and water consumption were not altered by compound exposure and liver weights (the only organ for which weights were obtained) was not altered in dosed groups compared to controls. Mean group maternal body weight gain was not affected in the LDT or MDT compared to controls but was reduced 26% during the period of dosing (gestation days 6-15) in the HDT. This effect appeared to transient though, as the HDT group had weight gain similar to the other groups in the post-treatment period (gestation days 16-21).Clinical signs of toxicity were evident at the HDT only. Excessive salivation, perineal urine stains, peri-ocular porphyrin deposits, vaginal bleeding, and tremors were noted throughout the dosing period in the HDT. Most cesarean section parameters were not altered by compound exposure. The only parameter that was altered was the pre-implantation loss. Pre-implantation loss in the controls was 5.3% while it was 9.4, 7.2 and 17% in the LDT, MDT and HDT groups respectively. Inhibition of cholinesterase activity was seen in the MDT and HDT groups. Plasma cholinesterase activity was decreased from 44.73 μ/ml in the controls to 4.28 and 1.56 μ/ml in the MDT and HDT respectively (these represent inhibitions of 90.3% and 96.5%, respectively). Erythrocyte cholinesterase activity was reduced from 11.98 μ/ml in the controls to 3.07 and 2.51 μ/ml in the MDT and HDT respectively (this represents inhibitions of 74.3% and 79%). The cholinesterase values for the LDT were similar to controls with plasma being 42.28 and erythrocyte being 11.85 μ/ml.

The systemic maternal LOAEL is 15 mg/kg/day, based on clinical signs such as salivation, and tremors. The systemic maternal NOAEL is 3.0 mg/kg/day. The maternal cholinesterase LOAEL is 3.0 mg/kg/day based on statistically significant decreases in erythrocyte and plasma cholinesterase activity. The maternal cholinesterase NOAEL is 0.1 mg/kg/day.

External examinations, visceral examinations and skeletal examinations did not reveal an increase in variations or malformations. There were no treatment-related effects in developmental parameters seen at any dose.

The developmental NOAEL is 15 mg/kg/day. The developmental LOAEL was not determined. This study is classified as acceptable/guideline.

In a developmental toxicity study (MRID 00095268), female CF-1 mice were administered chlorpyrifos by gavage on gestation days 6-15 at doses of 0, 1, 10, and 25 mg/kg/day (Experiment I). Because of severe maternal toxicity in the high dose group, additional groups of mice were exposed to 0, 0.1, 1.0, or 10 mg/kg/day on gestation days 6-15, inclusive (Experiment II). Maternal toxicity in the form of increased mortality (0/51, 1/40, 1/44, and 4/47 [$p<0.05$] at 0, 1, 10, and 25 mg/kg/day) and an increase in the number of mice showing clinical signs (0/51, 2/40, 9/44, and 32/47 at the above doses) were reported. Fetotoxicity was observed only at 25 mg/kg/day (decreased fetal body measurements and an increased incidence of minor skeletal variants). To determine the degree of RBC and plasma cholinesterase depression, additional groups of 4-10 mice were given 0, 1, 10, or 25 mg/kg/day of chlorpyrifos on day 6, days 6 through 10, or days 6 through 15 of gestation. Additionally, groups of 6-15 mice were given 0, 0.1, 1.0 or 10.0 mg/kg/day of chlorpyrifos concurrently with the animals for the low dose study (Experiment II) on day 6, days 6-10, or days 6 through 15 of gestation. Five hours after the final dosing (day 6, 10 or 15 of gestation, respectively), blood was obtained by cardiac puncture. A homogenate of fetuses from the mice sacrificed on day 15 of gestation was prepared to measure total fetal cholinesterase levels. Plasma cholinesterase levels decreased significantly in mice given 1, 10 or 25 mg/kg of chlorpyrifos on day 6, days 6 through 10, or days 6 through 15 of gestation. RBC cholinesterase levels also decreased significantly in mice given 10 or 25 mg/kg on day 6, days 6 through 10, or days 6 through 15 of gestation. Among mice given 1 mg/kg of chlorpyrifos on days 6 through 10 of gestation, a statistically significant decrease in RBC cholinesterase levels as compared to controls was observed. The fetal cholinesterase levels were decreased in fetuses from dams given 10 or 25 mg/kg of test material on days 6 through 15 of gestation.

The maternal LOAEL is 25 mg/kg/day, based on increased mortality and increased number of mice with clinical signs of cholinesterase inhibition. The maternal NOAEL is 10 mg/kg/day. The developmental LOAEL is 25 mg/kg/day, based on decreased fetal body measurements and increased incidence of minor skeletal variants. The developmental NOAEL is 10 mg/kg/day. The NOAEL for plasma and red blood cells cholinesterase is 0.10 mg/kg/day. This study is classified as unacceptable/non-guideline.

870.3700b Prenatal Developmental Toxicity Study – Rabbit

Chlorpyrifos was dosed via gavage at 0, 1, 9, 81, and 140 mg/kg/day to New Zealand rabbits for gestation days 7-19 (MRID 40436408).

Based on ChE inhibition the maternal NOAEL = 81 mg/kg with the maternal LOAEL = 140 mg/kg (based on decreased food consumption on gestation days 15-19; body weight loss during the dosing period followed by a compensatory weight gain; suggestion of post-implantation loss). The developmental NOAEL = 81 mg/kg/day with the LOAEL = 140 mg/kg/day (based on slight reduction fetal weights and crown-rump lengths; increased incidence of unmodified 5 th sternebra and/or xiphistrnum). The study is classified as acceptable/guideline.

A.4.3 Reproductive Toxicity

870.3800 Reproduction and Fertility Effects – Rat

In a two-generation reproduction study (MRID 41930301) chlorpyrifos (97.8-98.5% a.i.) was administered to 30 Sprague Dawley rats/sex/dose via the diet at dose levels of 0, 0.1, 1 and 5 mg/kg/day during the pre-mating period of 10 or 12 weeks (F_0 or F_1 generation, respectively); with exposure continuing in dams through gestation, lactation and weaning. The F_0-generation rats were mated once to produce F_1 litters. Plasma, red blood and brain cholinesterase (ChE) activity were determined for the first 10 F_0 and F_1 adult rats/sex/dose at the scheduled necropsy.

There were no treatment related effects on mortality, food consumption or clinical signs in either F_0 or F_1 animals. Parental toxicity was observed at 1 and 5 mg/kg/day as indicated by significant dose-related reductions in the ChE activities of the plasma (43-72% inhibition), and red blood cells (65-75% inhibition) in the F_0 and F_1 male and female adult rats. In addition, significant inhibition of brain ChE was noted in the high dose F_0 adult male and females (48 and 49% inhibition, respectively) and high dose F_1 males and females (53 and 58% inhibition, respectively). Parental F_0 and F_1 rats exposed to 5 mg/kg/day developed histopathological lesions of the adrenal gland that were confined to the cells of the zona fasciculata and were characterized as very slight to slight vacuolation. Also, histological changes in the adrenal gland were consistent with fatty changes in males and altered tinctorial properties in females. The body weights of the adult F_1 males were slightly lower than controls throughout the study in the 5 mg/kg/day dose group.

Neonatal effects were observed only in the presence of maternal toxicity and consisted of reduced pup weights and increased mortality at 5 mg/kg/day. There were no treatment-related effects on other reproductive parameters such as fertility indices, length of gestation, time to mating, pup sex ratio, pup survival, or litter size in either generation.

The NOAEL and LOAEL for parental toxicity are 0.1 and 1 mg/kg/day, respectively based on significant plasma, and red blood cell cholinesterase inhibition. The NOAEL and LOAEL for neonatal effects are 1 and 5 mg/kg/day, respectively, based on decreased pup weight and increased pup mortality. This study is classified as acceptable/guideline.

Chlorpyrifos was dosed to 10 males and 20 females per group at 58 days of age at levels of 0, 0, 0.03, 0.1 and 0.3 mg/kg/day for 1st generation and 0, 0, 0.1, 0.3 and 1.0mg/kg/day for subsequent generations (MRID 00029064 & 00064934). For each mating, conducted at 118 days of age, the number of conceptions, litter size, still births, resorptions, number and size of pups weaned, pup weight and growth rate were examined., Necropsy was performed upon death and on 5 rats/sex/group of Fla, F2a and F3a pups. Histology was conducted on control and F3a pups. Maternal RBC and plasma cholinesterase activity was measured at the time of Cesarian delivery. Only the b litters were used for reproduction study.

No clinical signs of toxicity were observed in parents or offspring. No treatment related effect was found on mortality, body weight gain, food consumption, number of pups, mean litter size, sex ratios, mean litter weight, growth rate (to weaning), gross and histological examinations (on F3a pups). The parental NOAEL is 0.1 mg/kg/day and the LOAEL is 0.3 mg/kg/day based on plasma and RBC ChE inhibition. The reproductive NOAEL not determined and the LOAEL is >1 mg/kg/day. The viability and lactation indices were decreased for F2a, F2b and F3a litters from the 1.0 mg/kg groups. Fetotoxicity may have arisen through the maternal milk. RBC and plasma ChE activity was depressed above 0.3 mg/kg level for female and at 1.0 mg/kg for male. No maternal toxic sign to 1.0 mg/kg/day. Reproduction indices are all normal for dose up to 1.0 mg/kg. This study is classified as acceptable/guideline.

Chlorpyrifos was dosed at 0.5, 0.8, 1.2 mg/kg/day in Sprague-Dawley rats (MRID 00130401).

Although not meeting core requirements for a reproduction study (primarily due to limited gross and no histological examination), the study is adequate to establish that the NOAEL for neonatal survival is 1.2 mg/kg/day (HDT), the primary purpose of the study. The NOAEL for other reproductive parameters is also 1.2 mg/kg/day and the NOAEL for general toxicity is 0.8 mg/kg/day based on decreased weight gain observed in the 1.2 mg/kg/day male dose level. In combination with the previous reproduction study (MRID No. 00029064 & 00064934), this study is adequate to meet the requirement for a core-minimum study.

A.4.4 Chronic Toxicity

870.4100a (870.4300) Chronic Toxicity

Chlorpyrifos was dosed to CD-1 mice at 0, 0.5 and 15 ppm for 2 years (MRID 00054352).

The systemic and oncogenic NOAEL was 2.25 mg/kg/day based on decreases in ChE activity of 90% in plasma and 50% in RBC. The study LOAEL values were not determined. The study is classified as acceptable and satisfies the requirement when taken together with MRID 00142902.

870.4100b Chronic Toxicity – Dog

The chronic toxicity study (MRIDs 00064933, 00146519) in dogs consisted of two phases. In Phase A, chlorpyrifos (97.2-98.8% a.i) as Dowco® 179 was administered to 3 beagle dogs/sex/dose in diet at dose levels of 0, 0.01, 0.03, 0.1, 1 or 3 mg/kg/day for one year (Phase A). One dog/group was sacrificed at one year, and the remaining 2 dogs/group were sacrificed after a 3 month recovery period. In Phase B, chlorpyrifos was administered to 4 beagle dogs/sex/dose at the same dose levels for a total of two years (Phase B), at which time all dogs were sacrificed.

The NOAEL and LOAEL for plasma ChE inhibition are 0.01 and 0.03 mg/kg/day based on consistent mean inhibition of 10% to 29% at 0.03 mg/kg/day compared to controls for both males and females in Phases A and B. HED did not identify a NOAEL and LOAEL for RBC ChE inhibition due to inconsistencies in the data and the large standard deviations that confounded the interpretation of the data at lower dose levels. The NOAEL and LOAEL for brain ChE were 1 and 3 mg/kg/day. The systemic NOAEL and LOAEL are 1 and 3 mg/kg/day based on liver weight effects. The chronic toxicity study in dogs in conjunction with the addendum that contains supplemental information are classified as ACCEPTABLE-GUIDELINE.

A.4.5 Carcinogenicity

870.4200a Carcinogenicity Study – Rat

In a carcinogenicity toxicity study (MRID 42172802), chlorpyrifos (96.1% a.i) was administered to 55 Fisher F344 rats/sex/dose in diet at dose levels of 0, 0.2, 5 or 100 ppm (equivalent to approximately 0, 0.0132, 0.33, or 6.99 mg/kg/day for males and 0, 0.0146, 0.365 or 7.78 mg/kg/day for females, respectively) for 104 weeks. Plasma cholinesterase (ChE) activity (10/animals/sex/group) was measured on weeks 14, 32, 45, 78 and 104, while red blood cell (RBC) ChE activity (10/animals/sex/group) was measured at weeks 45, 78 and 104. Plasma, RBC and brain ChE activities were measured on 5 animals/sex/group at week 50 and in 10 animals/sex/group at terminal sacrifice.

Rats in the 100 ppm group exhibited significantly decreased body weights in both sexes, and a significant increased incidence of non-neoplastic lesions (cataracts and diffuse retinal atrophy) in females. Plasma ChE activity was significantly inhibited at 5 and 100 ppm in both sexes. Significant plasma cholinesterase inhibition in the 5 ppm group ranged from 15 to 51% throughout the study in both sexes. In females exposed to 0.2 ppm, red blood cell ChE was also significantly inhibited 42% at the 50 week sacrifice, but was elevated 14% at the terminal sacrifice. Red blood cell ChE was also significantly inhibited in the 50 week sacrifice for the 5 and 100 ppm females (39 and 45% ↓, respectively), but inhibition was less pronounced at the terminal sacrifice where inhibition was 11 and 18%, respectively. At the week 50 measurements, the decrease in RBC ChE activity in the treated groups appeared to be seriously influenced by the high control value (3891 U/g tissue) compared to the other control values which ranged from 2092 to 2586 U/g tissue. Therefore, the RBC ChE inhibition in females at 50 weeks is discounted because of the unusually high control value. Brain ChE was significantly

reduced in both high dose males and females at the 50 week and terminal sacrifices (57-80% ↓), but was not significantly decreased at the other doses. At terminal sacrifice, males in the high dose group had significantly lower absolute liver and kidney weights that were not significant after correction for body weight, and therefore were not considered treatment-related. There were no treatment related effects in mortality, clinical signs, food consumption, or hematology.

At the doses tested, there was no treatment related increase in tumor incidence when compared to controls. Dosing was considered adequate based on decreased body weights and the increased incidence of non-neoplastic lesions.

The LOAEL and NOAEL for plasma inhibition are 5 and 0.2 ppm, respectively (0.33 and 0.0132 mg/kg/day, respectively). The LOAEL and NOAEL for systemic effects of decreased body weights in both sexes, and increased incidence of cataracts and diffuse retinal atrophy in females are 100 and 5 ppm, respectively (6.99 and 0.33 mg/kg/day, respectively). This carcinogenicity study in rats is classified as ACCEPTABLE-GUIDELINE.

In a chronic toxicity/carcinogenicity study (MRID 40952802), chlorpyrifos (98.5% a.i) was administered to 50 Fisher F344 rats/sex/dose in diet at dose levels of 0, 0.05, 0.1, 1 or 10 mg/kg/day for 104 weeks. Ten additional rats/sex/group were randomly allocated for the 12-month sacrifice. Plasma and red blood cell (RBC) cholinesterase (ChE) activities (10/animals/sex/group) were measured at months 6, 12, 18 and 24. Brain ChE activities were also measured at the 12-month (10/rats/sex/dose) and 24 month (20 rats/sex/dose) scheduled sacrifices.

Rats in the 10 mg/kg/day group exhibited a slight, but significant decrease in body weights (2-9%) in both sexes. Body weight gain was approximately 90% of controls in males and comparable among females. Male rats in the high dose group had an increase in the size of the adrenal gland characterized microscopically by increased fatty vacuolation of the zonal fasciculata. In addition, males exhibited changes in clinical chemistry parameters (decreased serum cholesterol, total protein, and globulin), an increase in urine specific gravity, and a decrease in some common geriatric conditions (renal disease and biliary hyperplasia), which may be secondary changes and do not reflect any deleterious effect on a specific organ or the overall health of the animals. Similar, but less severe effects were noted in the high dose female rats. There were no significant differences in food consumption, or survival in either sex.

There was a dose-related (in most cases) decrease in ChE activity (plasma, red blood cell and brain) at each time point in both sexes. Plasma ChE was significantly inhibited in both sexes at the 1 mg/kg/day (39-86%) and 10 mg/kg/day (56-95%) dose levels throughout the study. Brain ChE was significantly decreased at both the 1 mg/kg/day (5-9%) and 10 mg/kg/day (58-61%) dose levels at the 12 month sacrifice, but was only statistically reduced in the 10 mg/kg/day dose group at termination (56-57%). In the 1 mg/kg/day dose group, brain ChE activities were increased 3% in males, and decreased 4% in females at the 24 month sacrifice. RBC ChE was significantly depressed at the 1 mg/kg/day (14-34%) and 10 mg/kg/day (24-37%) dose levels in males throughout the study, although statistical significance was not attained at 12-months, and the value in the 1 mg/kg/day males at termination was only 14% lower than the control value. In

females, mostly non significant RBC ChE inhibition ranged from 16-22% for the 1 mg/kg/day dose group and 18-40% for the 10 mg/kg/day dose group during the 12, 18 and 24 month sacrifices.

At the doses tested, there was no treatment related increase in tumor incidence when compared to controls. Dosing was considered adequate based on decreased body weights coupled with the significant inhibition of plasma, red blood cell and brain ChE.

The LOAEL and NOAEL for systemic effects are 10 and 1 mg/kg/day, respectively based on effects on the adrenal gland and clinical chemistry alterations in males. The LOAEL and NOAEL for significant plasma (39-86%) and brain (5-9%) cholinesterase inhibition are 1 and 0.1 mg/kg/day, respectively. **This combined chronic toxicity/oncogenicity study in rats is classified as ACCEPTABLE-GUIDELINE.**

870.4200b Carcinogenicity (Feeding) – Mouse

This study evaluated the oncogenic potential of test compound, at dietary concentrations of 0, 5.0, 50 or 250 ppm chlorpyrifos (equivalent to approximately: 0, 0.89, 8.84, or 45.2 mg/kg/d (M); and 0, 0.938, 9.79, or 48.1 mg/kg/d (F), respectively) when administered to CD-1 mice for 78 weeks (MRID 42534201).

Systemic toxicity was observed in high-dose animals and included decreased body weight and feed consumption in males, lower mean water consumption in females, increased incidence of gross clinical findings (ocular opacity, hair loss on head and around eyes) and non-neoplastic lesions (keratitis, hepatocytic fatty vacuolation) in high dose males & females. Neoplastic lesions were observed in both sexes, but were not considered to be treatment-related. Plasma cholinesterase activities were significantly reduced at all treatment levels; brain activities were significantly decreased only in the high-dose animals.

The systemic NOAEL = 50 ppm (MDT). Systemic LOAEL = 250 ppm (HDT), based on decreased body weight in males, increase incidences of non-neoplastic lesions in males & females. Results of the study showed that the test compound does not have oncogenic potential. This study satisfies guideline requirements for an oncogenicity study in mice.

A.4.6 Mutagenicity

870.5100 Gene Mutation Bacterial Cell

Chlorpyrifos was tested in Salmonella strains TA 98, TA 100, TA 1535, TA 1537 and TA 1538 in the presence and absence of S-9 at concentrations of 30, 100, 300, 1000, 3000 and 10000 µg/plate (MRID 00157058 and 40436410). DMSO was the solvent and negative control. The positive controls were sodium azide, 9-aminoacridine, 2-nitrofluorene and 2-anthramine.

Chlorpyrifos was not toxic nor did it appear to increase over control values the number of revertant colonies/plate. Positive controls caused appropriate mutagenic responses. These studies were classified as Acceptable/Guideline.

870.5300 Gene Mutation Mammalian Cell

Chlorpyrifos was tested for gene mutation potential at 0, 10, 20, 25, 30, 40 & 50 µM in mammalian cells (MRID 00152683).

Chlorpyrifos was cytotoxic at 10 µM and above without metabolic activation and no toxicity with activation. Precipitate formed at 30 µM and higher concentrations with or without activation. Chlorpyrifos was negative for gene mutation. This study is classified as acceptable/guideline.

Chlorpyrifos was tested for gene mutation potential at the following concentrations: nonactivation from 5-75 µg/ml and with activation from 30-1000 µg/ml (MRID 40436410). Testing in the cytotoxicity assays at the following conditions: nonactivation from 1.5-3746 µg/ml and with activation from 1.5-500 µg/ml. Positive controls were ethyl-methane sulfonate (nonactivated) and dimethylnitrosamine (activated).

Cytotoxicity was detected only in non-activated assays at 50 µg/ml. There was no evidence of mutation. This study is classified as acceptable/guideline.

870.5375 In Vitro Cytogenetics

Chlorpyrifos was tested in an in vitro chromosomal aberration assay with and without S-9 activation (MRID 40436409). Concentrations assayed were as follows with non-activation in the 10 hour assay at 1.56, 3.12, 5.2, 10.4, 15.6, 31.2, 52, 104 & 156 µg/ml and in the 19-20 hour assay at 0.975, 1.47, 2.93, 4.89, 9.75, 14.7, 29.3, 48.9, 97.5 & 147 µg/ml. Concentrations tested with activation in the two 10 hour assays were 1, 1.5, 3, 5, 10, 15, 30, 50 & 100 µg/ml and 2.95, 4.95, 9.85, 14.8, 29.6, 49.4, 98.5 & 296 µg/ml, plus concentrations for the 19-20 hour assay were 9.75, 14.7, 29.3, 48.9, 97.5, 147 & 293 µg/ml. Positive controls were mitomycin C (non-activation) and cyclophosphamide (activation).

Cytotoxicity was shown in both non-activated as well as in activated assays. Chlorpyrifos did not appear to cause chromosomal aberrations. Positive controls caused appropriate mutagenic response. This study was classified as Acceptable/guideline.

870.5395 Micronucleus Assay in Mammalian Erythrocytes

Chlorpyrifos was tested at levels of 0, 7, 22, 70 mg/kg by gavage in corn oil in the mouse (MRID 00152684).

Chlorpyrifos was negative for clastogenic effects. This study is classified as acceptable/guideline.

870.5500 DNA Repair Assay in Bacteria

Increased damage to bacterial DNA was detected (Study 256040). This study is classified as acceptable/guideline.

870.5550 Unscheduled DNA Synthesis in Hepatocytes

Chlorpyrifos was tested with concentrations from 10E-06 M to 10E-04 M in isolated rat hepatocytes (MRID 00157057).

Chlorpyrifos was negative for UDS in isolated rat hepatocytes under the conditions of this study. The high dose was cytotoxic and also formed a precipitate. This study is classified as acceptable/guideline.

870.5575 Mitotic Gene Conversion in Yeast

Increased recombination frequency was detected in yeast (Study 256040). This study is classified as acceptable/guideline.

A.4.7 Neurotoxicity

870.6100 Delayed Neurotoxicity Study – Hen

Chlorpyrifos was dosed at 0, 50, 100 or 110 mg/kg in hens (MRID 00097144 and 40510601).

There is no evidence of histopathologically observed neurotoxicity in hens. The NOAEL is 110 mg/kg, negative for neurotoxicity at 110 mg/kg. The LOAEL was not determined. The LD_{50} in hens = 106 mg/kg. These studies are classified as acceptable/guideline.

870.6200a Acute Neurotoxicity Screening Battery

Male & female Fischer 344 rats were treated once, by oral gavage, with chlorpyrifos at doses of 0, 10, 50 or 100 mg/kg and evaluated for neurotoxicity on days 1 (at the peak time of toxicity, approximately 6 hours after dosing), 8 and 15 (MRID 42669101 and 42943101).

Systemic toxicity consisted of decreased body weights of animals in the 50 and 100 mg/kg groups. Neurotoxic effects consisted of decreased motor activity on day 1 through day 8 (females only). Significant FOB changes were limited to high dose females, of which 6 out of 10 could not perform the landing hind leg splay on day 1 of the study. Grip performance on day 1 revealed a possible treatment-related decrease with increasing dose. Neuropathological examinations did not reveal any treatment-related effects. Systemic NOAEL (M&F) = 10 mg/kg (LDT) with the systemic LOAEL (M&F) = 50 mg/kg (MDT). LOAEL is based on decrease in both body weight and motor activity and increased incidence of adverse clinical signs consistent with organophosphorus intoxication. These studies are classified as guideline.

870.6200b Sub-chronic Neurotoxicity Screening Battery

In this sub-chronic neurotoxicity study, male and female Fischer 344 rats were treated for 13 weeks with diets containing sufficient chlorpyrifos to yield doses of 0, 0.1, 1.0, 5.0 or 15 mg/kg/day (MRID 42929801). During the study, body weights, clinical signs, FOB, motor activity and neuropathology were examined. FOB, performed at pre-study and weeks 4, 8, 13 consisted of hand-held and open field observations and measurement of grip performance and landing foot splay.

The study indicated the treatment-related effects included decreased motor activity and an increased incidence of urine incontinence on females. Although a statistically significant depression in motor activity was present in high-dose animals at week 4. The transitory nature of the effect suggests that the differences were not treatment-related. In addition, a low, and statistically non-significant, increase in the incidence of urine incontinence was observed in several 5 and 15 mg/kg/day females during the clinical examinations and FOB evaluations. One high-dose female showed urine incontinence at weeks 4, 8, and 13 and another, only at weeks 4 and 8. None of the other animals showed urine incontinence in more than one FOB session. There was no clear dose- or time-relationships which would suggest that the incontinence was treatment-related. Body weights of treated animals were comparable to controls. Neuropathological examination did not reveal any differences which might be attributed to treatment. No neurotoxicity was noted at 15 mg/kg/day, a dose previously shown to markedly inhibit plasma (>80%), RBC (>45%) and brain (>62%) cholinesterase activities.

The NOAEL for neurotoxicity was established at 15 mg/kg/day (high dose tested); the LOAEL was not established. This study is satisfies guideline requirements for a sub-chronic neurotoxicity screening battery in the rat.

870.6300 Developmental Neurotoxicity Study

In this developmental neurotoxicity study (MRID 44556901 and companion 44648101 cholinesterase study), 25 pregnant Sprague-Dawley rats/group were administered chlorpyrifos (99.8% a.i.) by gavage from gestation day 6 (GD 6) through lactation day 11 at 0, 0.3, 1, or 5 mg/kg/day. An additional 5 pregnant females/group were dosed at the same levels for the cholinesterase (ChE) phase of the study. Dams were examined for body weight, reproductive performance, number of viable pups, and postpartum behavior. During the dosing period, dams were observed daily for signs of autonomic function toxicity. Satellite dams were sacrificed four to five hours post-dosing on GD 20 for ChE analyses to be performed on brain, plasma, and erythrocytes. Offspring were examined for viability at birth, pup/litter survival, body weight, sex ratio, physical development landmarks (eye opening and pinna detachment), observed nursing behavior, and sexual maturation. F_1 generation litters were randomly standardized on lactation day 5 and assigned to 4 subsets for continued observation. On postnatal day (PND) 12, fixed brain weight measurements (10 pups/sex/dose) and neuropathological evaluations including morphometrics (6 pups/sex/dose) were performed on Subset 1 pups, with the remaining 10 pups/sex/dose necropsied for gross lesions. In Subset 2, 8 pups/sex/dose were selected for evaluation of learning and memory; evaluations were performed on PNDs 23-25 and 62-92. These Subset 2 animals were sacrificed on PNDs 97-101, following the last evaluation. The Subset 2 pups not selected for evaluation were necropsied for gross lesions on PND 22. The

Subset 3 pups were tested for motor activity on PNDs 14, 18, 22, and 61 and auditory startle habituation on PNDs 23 and 62; all Subset 3 animals were sacrificed on PNDs 63 or 64 following the last evaluation. In Subset 4 pups, fixed brain weights were determined in 10 pups/sex/dose, neuropathological examinations were performed on 6 pups/sex/dose, and all remaining Subset 4 animals (10/sex/dose) were necropsied for gross lesions upon sacrifice on PND 66-77.

Maternal toxicity in the high-dose (5 mg/kg/day) animals was manifested as increased signs of autonomic function toxicity, apparent at the end of gestation as fasciculations (6/25 treated vs 0/25 controls), and during early lactation (days 1-5) as fasciculations (16/24 treated vs 0/25 controls), hyperpnea (8/24 treated vs 0/25 controls), and hyperreactivity (17/24 treated vs 2/25 controls). Dams with all pups dying were increased in the high-dose group (3/23 treated vs 0/25 controls). There were no significant effects on bodyweight, food consumption, or pregnancy parameters. There were no unscheduled deaths in the maternal animals.

Brain ChE activity was decreased in the high-dose (↓90%) and mid-dose (↓18%) dams as compared to control. Erythrocyte (↓41-99%) and plasma (↓43-92%) ChE activities were decreased in a dose-dependent manner in all treated groups.

For the F_1 generation pups, the high-dose group bodyweights were significantly reduced (↓8-15%) at PND 1 and 5 (pre- and post-culling). Bodyweights were also reduced from birth to PND 22 in Subset 4 high-dose animals (↓5-19%); bodyweight gains were reduced in these animals during the same period (↓5-30%). Additionally, compared to the controls, reduced terminal body weights were observed in the Subset 1 (PND 12) high-dose animals (↓17-19%) and the Subset 4 (PND 66) high-dose males (↓10%). For the F_1 generation adults, body weights of the high-dose males were decreased at PND 22 through 66 (↓11-17% vs controls). High-dose F_1 adult females also weighed less than controls at PND 22 (↓17% vs controls), but were of similar weight at PND 66. Bodyweight gains were also decreased in the high-dose males for the PND 22-40 interval (↓13% vs controls) and PND 40-66 interval (↓7%). Food consumption was decreased immediately after weaning (PND 23-30) in high-dose males and females (↓13% vs controls).

Development as assessed by pinna unfolding was delayed (4.0 days in treated vs 3.5 days in controls) in the high-dose group. Sexual maturation was delayed as assessed by time to preputial separation (106% of controls) and vaginal patency (103% of controls).

Pup viability was reduced as assessed by the following parameters: surviving pups/ litter (↓27%) and live litter size at culling (↓16%), pup viability index (↓29%), and pups found dead or presumed cannibalized (day 1 - 7.2 % treated vs 0.0% controls; days 2 to 5 - 24.7% treated vs 1.3% controls).

There were no statistically significant differences between the groups in the average acquisition and delay training. Additionally, there were no differences among dose groups when comparing retention of information during PNDs 23-25 and 62-92. Motor activity was decreased in high dose male and female pups on PND 14 (↓56% in males and ↓37% in females), and increased in

high dose females on PNDs 18 and 22 (↑51% on both days). On PND 61, motor activity was increased for both sexes (↑16-17%). There was a statistically significant increase (↑16-25%) in the latency to peak response during the auditory startle habituation assessments on PND 23 in the high-dose animals compared to concurrent controls. At PND 62, the latency to peak response in the high-dose animals was 10-12% higher than in the controls. Additionally, the peak response amplitudes in the high-dose animals were decreased by 9 to 29% on PNDs 23 and 62 (not statistically significant) compared to the controls.

There were no gross or microscopic lesions of the nervous system in Subset 1 or 4 offspring. Subset 1 high-dose males at PND 12 had reduced absolute brain weights (↓9% vs controls), increased relative brain weights (↑13% vs controls), reduced anterior to posterior measurement of the cerebellum (↓24% vs controls), reduced height of the cerebellum (↓14% vs controls), decreased thickness of the parietal cortex (↓6% vs controls), and decreased thickness of the hippocampal gyrus (↓9% vs controls). High-dose female pups had reduced absolute brain weights (↓9% vs controls), increased relative brain weights (↑14% vs controls), decreased thickness of the parietal cortex (↓6% vs controls), decreased width of the caudate-putamen (↓10% vs controls), and decreased thickness of the hippocampal gyrus (↓12% vs controls). In Subset 4 F1 animals, killed on PND 66, morphometric analysis revealed significantly decreased parietal cortex measurements in high-dose (↓5%) and mid-dose (↓4%) females, as compared to controls. Decreases in the thickness of the hippocampal gyrus in high-dose females (↓7%) resulted in contradictory statistical results when compared to controls; decreases in mid-dose (↓4%) females as compared to control were not found to be statistically significant. There was no evaluation of the morphometric data for low dose females at PND 66. Brain weight in high dose females was similar to control brain weight at day 66 (↓0.3%).

It is not possible to definitively classify findings in the preweaning offspring as having originated with pre- or postnatal exposure, nor as resulting from developmental perturbation versus direct systemic- or neurotoxicity. However, adverse findings in the adult (~PND 66) offspring, i.e., alterations in motor activity, auditory startle response, and brain structure (decreased measurements of the parietal cortex and hippocampal gyrus, in the absence of brain weight deficits) can be interpreted to represent the long-term sequellae of developmental exposure to chlorpyrifos.

Adverse effects in the offspring have been identified at the MDT of 1.0 mg/kg/day; these include a significant treatment-related decrease in the measurement of the parietal cortex, supported by possible (although non-significant) alterations in the hippocampal gyrus, in the brain of female rats at postnatal day 66.

The maternal toxicity NOAEL was not observed. The maternal LOAEL was < 0.3 mg/kg/day, based on plasma and RBC cholinesterase inhibition. However, due to the lack of morphometric data for low-dose (0.3 mg/kg/day) female rats at postnatal day 66, the offspring NOAEL and LOAEL cannot be determined. This study has been classified as guideline/unacceptable (but upgradeable).

A.4.8 Metabolism

870.7485 Metabolism – Rat

This study (MRID 44648102) was done to help construct and validate a physiologically-based pharmacokinetic model for chlorpyrifos (Unlabeled - 99.8% a.i., Lot # MM930503-17; Labeled - 89.4% a.i., Lot # B930-51 [INV1134]) a weak inhibitor of acetylcholinesterase activity, and its metabolites, chlorpyrifos-oxon (OXON), a strong cholinesterase inhibitor and 3,5,6-trichloropyridinol. Groups of 24 male rats were given a single gavage dose of 0.5, 1, 5, 10, 50, or 100 mg/kg chlorpyrifos in corn oil. Four rats from each group were killed 10 and 20 minutes and 1, 3, 6, and 12 hours after treatment. Cholinesterase activity was measured in the brain and plasma at each time point, as well as the plasma concentration of the test material and its OXON metabolite. In a separate portion of the study, four male rats were given a single gavage dose of labeled chlorpyrifos at a concentration of 5 or 100.0 mg/kg and were sacrificed three hours later. Blood was collected from the animals at sacrifice and the concentration of the test material and its metabolites 3,5,6-trichloropyridinol (TCP) and OXON determined.

Plasma cholinesterase activity decreased in a time- and dose-dependent manner. The plasma cholinesterase activities of rats treated with 0.5, 1, 5 or 10 mg/kg were maximally decreased 3-6 hours after treatment, with both the decrease and recovery of activity being dose-dependent. The decrease in activity of rats treated with 50 or 100 mg/kg began within 10 minutes of treatment. By 12 hours after treatment, both groups were approximately 11% of the control group and had not shown signs of recovery.

Brain cholinesterase activity was not affected as dramatically by test material treatment as plasma activity with only the 10, 50, and 100 mg/kg dose groups showing significant effects. The brain cholinesterase activity in the 50 or 100 mg/kg dose groups decreased significantly within one hour of treatment; mirrored each other; and by 12 hours, were approximately 30% and 20%, respectively, of control. The brain cholinesterase activity of rats treated with 10 mg/kg test material began to decline within three hours of treatment and was significantly decreased by six hours after treatment. In none of the affected groups did brain cholinesterase show signs of recovery.

Peak chlorpyrifos blood concentrations occurred within three hours of treatment in all but the lowest dose group. The area under the curve (AUC) was calculated as 0.4, 1.1, 5.0, and 12.5 µmole hr L-1 for the 5.0, 10.0, 50.0, and 100 mg/kg groups, respectively and yielded calculated blood half-lives of chlorpyrifos of 2.7,1.5, 2.1, and 7.3 hours for the 5.0, 10.0, 50.0, and 100.0 mg/kg dose groups, respectively. Regardless of dose, the highest concentration of OXON detected was 2.5 ng/g found in the blood of rats treated with 50 mg/kg test material one hour post-treatment. Following treatment with 5 or 100 mg/kg labeled test material, >=98% of the activity detected in the blood was identified as TCP metabolite with the remaining attributed to the parent compound. Since OXON is an intermediate in the formation of TCP and none of the metabolite was detected, these studies support that the half-life of the OXON metabolite is short (reportedly 10 seconds) and that in vivo metabolism of chlorpyrifos is rapid.

This study is considered acceptable (non-guideline).). It may partially fulfill guideline

requirements in other areas.

In another study of tissue distribution and metabolism (MRID 40458901), carbon-14 labelled chlorpyrifos was administered orally to Fischer 344 rats for 15 days (MRID 40458901).

The majority of the radioactivity was recovered in the urine (>84%) and feces (>5%) within 72 hours. Less than 0.2% of the radioactivity remained in tissues and carcass. No unchanged chlorpyrifos was found in the urine and the main urinary metabolites were identified as 3,5,6-TCP and conjugates (glucuronide and possibly sulfate) of 3,5,6-TCP.

This study is classified as acceptable-guideline.

870.7600 Dermal Absorption

Single doses of 0.5 mg/kg (N=1) and 5.0 mg/kg (N=5) of chlorpyrifos were administered to male humans (accession No. 249203).

Based on the urinary excretion of the 3,5,6-TCP metabolite, the minimum absorption was approximately 1-3% dermally. The proportion of the administered dose metabolized to this pyridinol is unknown, these estimates are considered minimum values (i.e. absorption could be higher).

A.4.9 Immunotoxicity

870.7800 Immunotoxicity

In an immunotoxicity study (MRID 48139304), chlorpyrifos technical (99.8% a.i., Lot No. KC28161419) was administered in the diet to 10 female Crl:CD(SD) rats/dose at nominal dose levels of 0, 0.4, 2, or 10 mg/kg/day (actual dose levels of 0, 0.416, 2.13, or 10.7 mg/kg/day) for 28 days. The female rat was determined to be the appropriate test species/sex for this study. Cyclophosphamide in sterile saline was intra-peritoneally administered to the positive control group on Days 24 to 28 at a rate of 20 mg/kg body weight/day. On Day 24, all animals received a 0.5 mL intravenous injection of sheep red blood cells (SRBCs) in isotonic saline (2×10^8 SRBCs)/mL). T-cell dependent antibody response (TDAR) was evaluated at day 29.

There were no statistically significant effects of treatment with chlorpyrifos on mean body weights, body weight gains, or food consumption. Statistically significant decreases in mean red blood cell (RBC) cholinesterase (ChE) activity were seen in all test substance treatment groups. Mean brain ChE activity was significantly decreased in the mid- and high-dose groups. There were no test substance treatment-related effects on clinical signs, gross anatomy, or hematological parameters. In the positive control group, mean body weights and body weight gains were lower than the control value throughout the study; these differences were attributed to normal body weight variability. No unscheduled mortalities occurred in any study group. For systemic toxicity related to treatment with chlorpyrifos, the NOAEL for female rats is 10 mg/kg/day (highest dose tested) based on no effects were seen in clinical observations, body

weight, food consumption, and hematological parameters. The LOAEL for systemic toxicity was not established. For neurotoxic effects, the LOAEL for female rats is 0.4 mg/kg/day (lowest dose tested), based on decreased RBC cholinesterase activity. The NOAEL for neurotoxic effects was not established (i.e., less than 0.4 mg/kg/day).

For immunotoxicity, there were no treatment-related effects on mean absolute and relative spleen and thymus weights or hematological parameters at any dose level. The anti-SRBC IgM titers did not show statistically significant differences among treatment and the control groups. Decreased anti-SRBC titers for the 2 and 10 mg/kg/day treatment groups (64% and 41%, respectively) were observed when compared with the control. However, the decreased response in these dose groups may have been due, in part, to a high mean value for the control group. The biological significance of these observations also was confounded by the lack of a clear dose response (the decrease was greater for the mid-dose group than for the high-dose group). The positive control demonstrated the validity of the assay. Considered the trend and distribution of individual animal data in treatment and control groups, there was no significant suppression of the anti-SRBC titers with chlorpyrifos exposure.

The NK cell activity was not evaluated. There were no treatment-related effects on spleen and thymus weights and histopathology parameters that would suggest the potential for immunotoxicity in repeat-dose studies (2-week, 28-day, 90-day, 2-year) studies in rats and mice. Under HED guidance, if the TDAR assay is negative and evaluation of observational endpoints from all available toxicology database provide no evidence of immunotoxicity, the test article is considered negative for immunotoxicity and evaluation of NK activity is not necessary.

Under conditions of this study, the NOAEL is 10 mg/kg/day (highest dose tested) based on the overall weight-of-evidence. A lack of dose-related response for anti-SRBC IgM titers at the mid- and high-dose levels, a lack of statistical significance at any dose level, and a lack of evidence of other immunological effects (absolute and relative spleen and thymus weights, hematological parameters). A LOAEL for immunotoxicity was not established. This immunotoxicity study in the rat is considered as acceptable/guideline and satisfies the guideline requirement for an immunotoxicity study (OPPTS 870.7800) in rats.

A.4.10 Special/Other Studies

Comparative Cholinesterase Assay

Comparison of cholinesterase (ChE) inhibition in young adult and preweanling CD rats after acute and repeated chlorpyrifos exposures were performed (MRID 48139301).

The following table illustrates the NOAEL and LOAELs derived from the acute dosing aspects of this study. Male pups had the same NOAELs and LOAELs as female pups.

Enzyme Source	Acute NOAEL/LOAEL mg/kg (% Inhibition at LOAEL) Pups (male/female %)	Adults (females only)
Plasma ChE:		
CPY – gavage	0.5/2(51%/47%)	0.5/2(54%)
CPY – milk/diet	0.5/2(39%/44%)	0.5/2(58%)
CPO - gavage	0.05/0.1(18%/21% but 51% at 0.5 mg/kg)	0.1/0.5(56%)
RBC AChE:		
CPY – gavage	0.5/2(35% /31%)	0.5/2(19%)
CPY – milk/diet	0.5/2(29%/27%)/	0.5/2(52%)
CPO - gavage	0.1/0.5(46%/47%)	0.1/0.5(36%)
Brain:		
CPY – gavage	2/5(51%/55%)	2/10(57%)
CPY – milk/diet	2/5(42%/56%)	2/10(22%)
CPO - gavage	Not inhibited	Not inhibited

Cpy = chlorpyrifos
CPO = chlorpyrifos oxon

The following table illustrates the NOAEL and LOAELs derived from the repeat dosing aspects of this study.

Enzyme Source	NOAEL/LOAEL mg/kg (% Inhibition at LOAEL) Pups	Adults
Plasma ChE:		
CPY	0.1/0.5(46%)	0.1/0.5 (46%)
CPO	0.01/0.5 (62%)	0.01/0.5 (76%)
RBC AChE:		
CPY	0.1/0.5 (18%)	0.1/0.5 (20%)
CPO	0.01/0.5 (84%)	0.01/0.5 (87%)
Brain:		
CPY	0.5/1 (19%)	0.5/1 (9%)
CPO	Not inhibited	Not inhibited

The classification of this *in vivo* comparative cholinesterase inhibition study is Acceptable/Non-Guideline.

Special Acute Neurotoxic Esterase Study in Rat

In a special study designed primarily to assess for the potential of chlorpyrifos to inhibit neurotoxic esterase (NTE), chlorpyrifos was administered by gavage to six groups of Fischer 344 strain female rats at dose levels of 0, 1, 5, 10, 50 or 100 mg/kg and sacrificed 24 hours later (MRID 44273901). NTE was assessed for by the method of Kayyali *et al* (J. Anal. Toxicol. 15:86-89 (1991). Dosing was by gavage at a dosing volume of 10 ml/kg. The rats were also assessed for cholinesterase inhibition in the plasma, red blood cells (RBCs), heart and brain and there was an additional group dosed at 0.5 mg/kg included for assessment of cholinesterase only.

The cholinesterase inhibition data indicated a NOAEL and LOAEL for plasma cholinesterase (ChE) and RBC and heart acetylcholinesterase (AChE) of 1 and 5 mg/kg, respectively. At 5 mg/kg, plasma ChE, RBC AChE and heart AChE were significantly inhibited approximately 45%, 17% and 19%, respectively. Brain AChE demonstrated a NOAEL and LOAEL of 10 and 50 mg/kg, respectively and at 50 mg/kg inhibition was approximately 53%. NTE was not inhibited at the highest dose level of 100 mg/kg and there was an apparent 9% increase in activity at this dose level.

This study is classified as ACCEPTABLE (Non-Guideline). The study contains data useful for evaluating the potential for chlorpyrifos to inhibit neurotoxic esterase following systemic administration.

Cognitive Rat Study

In this special study (MRID 44020901) the effects of repeated oral administration of chlorpyrifos technical (purity, 98.1%; lot no. #MM-890115-616) on the cognitive function of rats were evaluated with a delayed matching to position (DMTP) test. Groups of 10 female Long-Evans rats, pretrained in a DMTP apparatus were administered oral doses of chlorpyrifos in corn oil of 0, 1, 3, or 10 mg/kg/day for 5 days/week for 4 weeks. DMTP testing was conducted 6 days/week during treatment and continued post-dosing for 4 weeks. Testing for short-term memory (as evidenced by the retention rate) and attention/encoding deficits was based on the percent correct accuracy on several time delays. Slope over delay and intercept at time zero were calculated from these data for each rat and represented the "forgetting curve."

A satellite group of 6 rats/dose was sacrificed after the 4-week dosing period and plasma, erythrocyte and brain cholinesterase (ChE) were determined. Neurotoxic esterase (NTE) activity was determined in satellite rats from the control and high-dose groups one day after the last dose administration. Plasma (68%), RBC (56%) and brain (8%) ChE were inhibited at 1 mg/kg/day. At 3 mg/kg/day, plasma (83%), RBC (65%) and brain (63%) ChE inhibition was increased. At 10 mg/kg/day plasma (93%), RBC (65%) and brain (86%) ChE inhibition was further increased. NTE was minimally decreased (6%) in the high-dose group but this was not considered toxicologically significant. The clinical sign of miosis was observed in rats that received 3 and 10 mg/kg/day particularly at weeks 3 and 4. Salivation and tremors were observed primarily at 10 mg/kg/day with the tremors usually disappearing by the following morning.

A statistical analysis of the actual percent correct data was provided (supplemental report dated February 10, 1999) and no statistical differences (i.e., $p < 0.05$) indicative of treatment related decreases in percent correct choices were established for any dose or delay time. Thus, cognitive function is not obviously impaired. No consistent pattern in the intercept of the retention gradient was noted since it was increased at week 2 and decreased at week 3 but equivalent to the control at weeks 1 and 4 at 10 mg/kg/day. The DMTP parameters of actual total delay (increased by as much as 2.5 sec in the 0 delay trial at week 2), void trials per session (increased from about 5 in the control to about 15) and nosepokes (decreased ~42% at week 1 for the 15 sec delay) were affected in the 10 mg/kg/day Chlorpyrifos dose at most or all intervals during dosing. Although these effects can be possibly related to a decrease in motor activity known to be associated with organophosphates, the increase in void trials may also indicate a motivational or attention deficit.

The LOAEL for ChE inhibition is 1 mg/kg/day, with no NOAEL was established. The LOAEL for overt cholinergic signs is 3 mg/kg/day based on miosis. The NOAEL is 1 mg/kg/day. The LOAEL for DMTP performance (i.e. increase in void trials) is 10 mg/kg/day with the NOAEL at 3 mg/kg/day. This study is classified ACCEPTABLE (Non-guideline).

Acute Inhalation Study

Acute inhalation exposure of adult Crl:CD(SD) rats to particulate chlorpyrifos aerosols was assessed (MRID 48139303). The kinetics of concentration dependent cholinesterase (ChE) inhibition in red blood cells, plasma, brain and lung was measured. In the special acute inhalation study female rats were exposed nose only to atmospheric concentrations of up to mg/m^3 of particulate chlorpyrifos for six hours and allowed an additional 72 hours to recover (MRID No: 48139303 Hotchkiss *et al*. 2010). The peak inhibition for plasma and lung ChE was at 6 hours post-dosing. Significant lung (47%) and plasma (48%) ChE inhibition were noted at the lowest concentration tested of 3.7 mg/m^3, which is a LOAEL. RBC and brain ChE inhibition were noted at 12.9 mg/m^3 and 53.9 mg/m^3, respectively, indicating they are less sensitive than lung and plasma ChE inhibition following acute inhalation exposures. No NOAEL was established. EPA estimated a human equivalent concentration (HEC) of 0.62 mg/ m^3 based on the LOAEL of 3.7 mg/m3.

The LOAEL is 3.7 mg/m^3 based on lung cholinesterase testing (HEC of 0.62 mg/ m^3 estimated by EPA). A NOAEL was not identified. The classification of this special inhibition study is Acceptable/Non-Guideline.

Appendix B. Physical/Chemical Properties

Physicochemical Properties of Chlorpyrifos.		
Parameter	Value	Reference
Melting point/range	41.5-42.5 ºC	Chlorpyrifos IRED
pH	NR	
Density (21ºC)	1.51 g/mL	
Water solubility (25°C)	1.05 mg/L	
Solvent solubility (20°C)	Acetone >400 g/L Dichloromethane >400 g/L Methanol 250 g/L Ethyl acetate >400 g/L Toluene >400 g/L n-hexane >400 g/L	
Vapor pressure, (25°C)	$1.87x10^{-5}$ torr[1]	
Dissociation constant, pK_a	NR	
Octanol/water partition coefficient, $Log(K_{OW})$	4.7	
UV/visible absorption spectrum	NR	

NR – not reported.

[1] R. Bohaty, June 2011, D368388 and D389480, *Chlorpyrifos Drinking Water Assessment for Registration Review* (CRF assessment, Oct. 16, 2009 product chemistry BC 2062713)

Appendix C. Current US Tolerances and International Residue Limits

Chlorpyrifos (059101)

Summary of US and International Tolerances and Maximum Residue Limits				
Residue Definition:				
US	Canada		Mexico[2]	Codex[3]
40CFR180.342 chlorpyrifos *per se* (*O,O* -diethyl *O* -(3,5,6-trichloro-2-pyridyl) phosphorothioate	*O,O*-diethyl-*O*-(3,5,6-trichloro-2-pyridyl) phosphorothioate (apples, grapes, tomatoes) *O,O*-diethyl-*O*-(3,5,6- trichloro-2-pyridyl) phosphorothioate, including the metabolite 3,5,6-trichloro-2-pyridinol (citrus fruits; fat, kidney, and liver of cattle; kiwifruit; peppers; rutabagas; meat and meat byproducts of cattle (calculated on the fat content)			Chlorpyrifos. The residue is fat soluble.
Commodity[1,]	*Tolerance (ppm) /Maximum Residue Limit (mg/kg)*			
	US	Canada	Mexico[2]	Codex[3]
Alfalfa, forage	3.0			
Alfalfa, hay	13			5 alfalfa fodder
Almond	0.2			0.05
Almond, hulls	12			
Apple	0.01	0.01		1 pome fruits
Apple, wet pomace	0.02			
Banana	0.1			2
Beet, sugar, dried pulp	5.0			
Beet, sugar, molasses	15			
Beet, sugar, roots	1.0			0.05
Beet, sugar, tops	8.0			
Cattle, fat	0.3	1.0		
Cattle, meat	0.05	1.0		1 (fat)
Cattle, meat byproducts	0.05	1.0		0.01 cattle, kidney and liver
Cherry, sweet	1.0			
Cherry, tart	1.0			
Citrus, dried pulp	5.0			
Citrus, oil	20			
Corn, field, forage	8.0			
Corn, field, grain	0.05	0.05		0.05 maize
Corn, field, refined oil	0.25			0.2 maize oil, edible
Corn, field, stover	8.0			10 maize fodder (dry)
Corn, sweet, forage	8.0			
Corn, sweet, kernel plus cob with husk removed	0.05	0.05		0.01 sweet corn (corn-on-the-cob)
Corn, sweet, stover	8.0			
Cotton, undelinted seed	0.2			0.3 cotton seed
Cranberry	1.0			1
Cucumber	0.05	0.05		
Egg	0.01			0.01 (*)
Fig	0.01			

Summary of US and International Tolerances and Maximum Residue Limits				
Residue Definition:				
US	Canada		Mexico[2]	Codex[3]
Fruit, citrus, group 10	1.0	1.0		1
Goat, fat	0.2			
Goat, meat	0.05			
Goat, meat byproducts	0.05			
Hazelnut	0.2			
Hog, fat	0.2			
Hog, meat	0.05			0.02 (fat)
Hog, meat byproducts	0.05			0.01 (*) pig, edible offal
Horse, fat	0.25			
Horse, meat	0.25			
Horse, meat byproducts	0.25			
Kiwifruit	2.0	2.0		
Lettuce	1.0			
Milk, fat (Reflecting 0.01 ppm in whole milk)	0.25			0.02 milk
Nectarine	0.05	0.05		
Onion, bulb	0.5			0.2
Peach	0.05	0.05		0.5
Peanut	0.2			
Peanut, refined oil	0.2			
Pear	0.05			1 pome fruits
Pecan	0.2			0.05 (*)
Pepper	1.0	1.0		2 peppers sweet including pimento or pimiento); 20 peppers chili, dried
Peppermint, tops	0.8			
Peppermint, oil	8.0			
Plum, prune, fresh	0.05			0.5 plums (including prunes)
Poultry, fat	0.1			
Poultry, meat	0.1			0.01 (fat)
Poultry, meat byproducts	0.1			0.01 (*) poultry, edible offal
Pumpkin	0.05			
Radish	2.0			
Rutabaga	0.5	0.5		
Sheep, fat	0.2			
Sheep, meat	0.05			1 (fat)
Sheep, meat byproducts	0.05			0.01 sheep, edible offal
Spearmint, tops	0.8			
Spearmint, oil	8.0			
Sorghum, grain, forage	0.5			
Sorghum, grain, grain	0.5			0.5
Sorghum, grain, stover	2.0			2 sorghum straw and fodder, dry
Soybean, seed	0.3			0.1 soya bean (dry)
Strawberry	0.2			0.3

Summary of US and International Tolerances and Maximum Residue Limits				
Residue Definition:				
US	Canada		Mexico[2]	Codex[3]
Sunflower, seed	0.1	0.1		
Sweet potato, roots	0.05			
Turnip, roots	1.0			
Turnip, tops	0.3			
Vegetable, brassica, leafy, group 5	1.0			2 Broccoli 1 Cabbages, head 0.05 Cauliflower 1 Chinese cabbage (type pe-tsai)
Vegetable, legume, group 6 except soybean	0.05	0.05 lentils		0.01 common bean (pods and/or immature seeds); peas (pods and succulent=immature seeds)
Walnut	0.2			0.05 (*)
Wheat, forage	3.0			
Wheat, grain	0.5			0.5
Wheat, straw	6.0			5 wheat straw and fodder, dry
MRLs with No US Equivalents				
Grapes		0.01		0.5
Tomatoes		0.01		
Carrot				0.1
Coffee beans				0.05
Cotton seed oil, crude				0.05 (*)
Cotton seed oil, edible				0.05 (*)
Dried grapes (=currants, raisins and sultanas)				0.1
Potato				2
Rice				0.5
Soya bean oil, refined				0.03
Tea, green, black (black, fermented and dried)				2
Wheat flour				0.1
Completed: M. Negussie; 04/12/2011				

[1] Includes commodities listed in the CFR as of 4/12/11. The 40CFR 180.342 (a) (3) also stipulates that "a tolerance of 0.1 part per million is established for residues of chlorpyrifos, per se, in or on food commodities (other than those already covered by a higher tolerance as a result of use on growing crops) in food service establishments where food and food products are prepared and served, as a result of the application of chlorpyrifos in microencapsulated form."

[2] Mexico adopts US tolerances and/or Codex MRLs for its export purposes.

[3] * = absent at the limit of quantitation; Po = postharvest treatment, such as treatment of stored grains. PoP = processed postharvest treated commodity, such as processing of treated stored wheat. (fat) = to be measured on the fat portion of the sample. MRLs indicated as proposed have not been finalized by the CCPR and the CAC.

(c) *Tolerances with regional registrations.* Tolerances with regional registration, as defined in 180.1(m), are established for residues of the pesticide chlorpyrifos *per se* (*O,O* -diethyl- *O* -(3,5,6-trichloro-2-pyridyl) phosphorothioate) in or on the following food commodities:

Commodity	Parts per million	Canada	Codex
Asparagus	5.0		
Grape	0.01	0.01	0.5

In addition, the following tolerances for chlorpyrifos are recommended under registration review:

Recommended/Reassessed Tolerances for Chlorpyrifos			
Commodity	**Established Tolerance (ppm)**	**Recommended Tolerance (ppm)**	**Comments** ***Correct Commodity Definition***
Grain, aspirated fractions	NA	22	
Cotton, gin by-products	NA	15	

Appendix D. Review of Human Research

ORE:

The chlorpyrifos occupational residential exposure assessment relies in part on data from studies in which adult human subjects were intentionally exposed to a pesticide or other chemical. These studies, which comprise AHETF, ORETF and PHED, as well as the majority of chemical-specific handler exposure data were determined to require a review of their ethical conduct, have received that review, and have been determined to be ethical. The chemical-specific handler exposure studies that were determined to be ethical and suitable for use in risk assessment are: MRID 42974501, Shurdut, B.A. *et al*. (1993); MRID 43138102, Honeycutt, R.C. & Day, E.W. Jr. (1994); MRID 44739302, Knuteson *et al*. (1999); and MRID 43027901, Contardi *et al*. (1993). A single handler exposure study, "Evaluation of Chlorpyrifos Exposure to Workers During Loading and Application of Lorsban 15 % Granular Insecticide During Corn Planting (MRID 44483501)," was determined to have been conducted in a manner which prohibits its use by the Agency.

Toxicology:

Deliberate dosing studies in adult (non-pregnant) humans are available which measure AChE activity and urinary levels of chlorpyrifos and/or its metabolites. Results from Nolan *et al* (1982; MRID 124144) have been used by the Agency in estimating (i.e. back-calculating) chlorpyrifos exposure based on urinary levels of TCP. This study has also been used to derive a dermal absorption factor in humans. The Nolan *et al* (1982)) study was reviewed by the Human Studies Review Board (June 24-25, 2009; http://www.epa.gov/hsrb/jun-24-25-2009-public-meeting.htm) and found to be scientifically and ethically conducted. EPA also determined that the study was ethically acceptable. Both the FIFRA SAP and HSRB supported the Agency's proposal to use this study for purposes of characterizing biomonitoring studies but not for purposes of deriving points of departure or in directly estimating uncertainty factors. Another intentional human dosing study was reviewed by the June 2009 HSRB (Kisicki *et al* (1999), MRID 44811002) and the HSRB concluded that the study was scientifically (and ethically) conducted. However, EPA ethics review had determined that "EPA is forbidden by 40 CFR §26.1704 to rely on the Kisicki *et al.* study, MRID 44811002, in actions taken under FIFRA or §408 of FFDCA. It is possible that the circumstances and purposes for which you propose to consider it may be such that the provisions of 40 CFR §26.1706 for an exception to the prohibition in 40 CFR §26.1704 may be satisfied." (J. Carley memo dated 5/29/09; http://www.epa.gov/hsrb/files/1d6-ethics-rvw-kisicki-etal-060109.pdf). The Kisicki data has not been used in the preliminary chlorpyrifos human health risk assessment.

Appendix E. Summary Benchmark Dose Values

As a preliminary analysis, the Agency has conducted BMD modeling on selected AChE studies. These studies were selected based on the availability of at least two treatment groups in addition to a control group. In addition, these studies were selected as they represented a variety of ages, lifestages, and durations. In the acute pup studies the Agency has focused on those studies representing rat ages (PND 10 and older) concordant with human post-natal exposure (i.e, birth and older) and durations of exposure.

BMD modeling was not performed on the 21-day dermal study or the subchronic inhalation studies in the rat since the highest doses tested were NOAELs. The recent acute inhalation CCA study (MRID 48139303) was not amenable to BMD analysis because of variability in the data (large standard deviations) and significant inconsistencies in baseline measurements over time.

The Agency has used a decreasing exponential dose-response model similar to that used for the OP and *N*-methyl carbamate cumulative risk assessments and previously reviewed and supported by the FIFRA SAP on several occasions (FIFRA SAP 2001, 2002, 2005a, 2005b, 2008). As shown below, the Agency has used two versions of the decreasing exponential model—R-based code similar to that used in the NMC cumulative risk assessment and the USEPA Benchmark Dose Software, version 2.1.1 (BMDS). The R-based program was derived from software written using version 1.2.1 of the open source statistical programming language R, and is based on methods utilized in the cumulative risk assessments. The Agency's benchmark dose software (BMDS) exponential model includes a family of nested exponential models from which an optimal model (based on statistical and model criteria) can be determined. The flexibility of the nested exponential models is reflected by the number of parameters considered in the models.

OPP has most often used R-based code to develop BMDs for risk assessment of cholinesterase inhibiting pesticides. However, recently, the Agency's BMDS has implemented the decreasing exponential model. As OPP transitions to using BMDS primarily for single chemical assessments, both approaches may be used in some assessments. It is notable that the two approaches provide remarkably consistent results for the selected studies.

Consistent with risk assessment on other OP and NMCs compounds, the Agency has used a benchmark response (BMR) level of 10% and has thus calculated BMD_{10}s and $BMDL_{10}$s. The BMD_{10} is the estimated dose where AChE is inhibited by 10% compared to background. The $BMDL_{10}$ is the lower confidence bound on the BMD_{10}. Extensive analyses conducted as part of the OP cumulative risk assessment (USEPA, 2002) have demonstrated that 10% is a level that can be reliably measured in the majority of rat toxicity studies, and is generally at or near the limit of sensitivity for discerning a statistically significant decrease in AChE activity across the brain compartment and is a response level close to the background AChE level. The Agency uses the BMDL, not the BMD, for use as the PoD since the BMDL accounts for variability of the data (USEPA, 2000). The BMD_{10} provides a point of comparison across studies and the BMD_{10} provides the basis for determining Toxicity Adjustment Factors (TAFs) for chlorpyrifos-oxon. Tables 1-4 provide the results of the BMD analysis of the parent, while Tables 5-8 provide the

results of BMD analysis of the oxon.

Typically, studies submitted for pesticide registration and most studies from the public literature only measure brain and/or blood ChEs. It is rare for data from peripheral tissues to be available for consideration. Chlorpyrifos is unique in that multiple studies are available which provide such peripheral data (Appendix B). Tables 10-13 do not include BMD results for plasma ChE measures. Consistent with OPP's ChE policy, plasma ChE data from animals are used for risk assessment when RBC AChE data are not reliable and/or when peripheral AChE measures are not available. This is not the case for chlorpyrifos; reliable RBC and peripheral data are both available. Thus, the plasma data have not been considered for PoD determination. When conducting BMD analysis for RBC AChE inhibition, the Agency generally starts with the standard BMR of 10% but will consider 15% or 20% in some cases. However, in the case of chlorpyrifos, data from peripheral tissues (e.g., heart, lung, liver) show these tissues are similar in sensitivity to RBC AChE inhibition. As such, when using RBC AChE inhibition as a surrogate for such peripheral data, the BMR of 10% has been used.

For the re-evaluation of endpoint selection for the oral route, OPP considered the quality of the all available studies, both previous and new.

The most robust studies for determining the acute oral PoD are from a new comparative cholinesterase (CCA) study (MRID 48139301) in the rat conducted by the registrant and the results of cholinesterase (ChE) analyses in male PND17 rats performed by EPA's ORD (Moser *et al*, 2006). Both of these studies involved a wide range of doses and provided high quality AChE data. The results of published studies (e.g., Timchalk *et al*. 2006 and Zheng *et al*. 2000) add support the findings of the Dow CCA Study and Moser *et al* (2006).

Table 1. Results of BMD Modeling of Male and Female Rat Pup Brain and RBC ChE Inhibition following a Single Oral Dose of Chlorpyrifos

Dataset	Sex/age	Endpoint/Route	BMD Program/Software			
			R-based Program		EPA BMDS V2.1.1	
			BMD_{10}	$BMDL_{10}$	BMD_{10}	$BMDL_{10}$
Moser *et al*, 2006	Male PND 17	Brain ChE/ Acute Gavage	0.84	0.75	1.89[a]	1.54[a]
Moser *et al*, 2006	Male PND 17	Whole Blood ChE/Acute Gavage	0.38	0.35	0.62[b]	0.43[b]
CCA Study MRID 48139301	Male PND 11	Brain ChE/ Acute Gavage	2.13	1.51	2.13[c]	1.53[c]
CCA Study MRID 48139301	Male PND 11	RBC ChE/ Acute Gavage	0.83	0.66	0.82	0.65
CCA Study MRID 48139301	Male PND 11	Brain ChE/ Acute Milk	(no computation)[d]	(no computation)[d]	4.4	2.4
CCA Study MRID 48139301	Male PND 11	RBC ChE/ Acute Milk	0.5	0.35	0.47	0.36
CCA Study MRID 48139301	Female PND 11	Brain ChE/ Acute Gavage	2.17	1.53	2.18	1.56
CCA Study MRID 48139301	Female PND 11	RBC ChE/ Acute Gavage	0.97	0.76	0.96	0.75
CCA Study MRID 48139301	Female PND 11	Brain ChE/ Acute Milk	1.53	1.03	1.42	0.91
CCA Study MRID 48139301	Female PND 11	RBC ChE/ Acute Milk	0.5	0.35	0.5	0.36

[a]High dose dropped to improve fit.
[b] High dose dropped to improve fit.
[c] P = 0.071.
[d] No computation (technical issues e.g., no convergence).

Table 2. Results of BMD Modeling of Adult Female Rat Brain and RBC ChE Inhibition following a Single Oral Dose of Chlorpyrifos

Dataset	Sex/route	Endpoint/ Route	BMD Program			
			R-based Single-Sex		EPA BMDS V2.1	
			BMD_{10}	$BMDL_{10}$	BMD_{10}	$BMDL_{10}$
CCA MRID 48139301	Adult Female Acute Gavage (8 hr)	Brain	No convergence	No convergence	4.11[a]	2.26[a]
CCA MRID 48139301	Adult Female Acute Gavage (8 hr)	RBC	1.5	1.13	1.9[b]	1.2[b]
CCA MRID 48139301 (a)	Adult Female 12 hr diet (6 pm-6 am)	Brain	(no computation)[c]	(no computation)[c]	4.47 (8 hr after feeding; 20 hr after food introduction)	3.30 (8 hr after feeding; 20 hr after food introduction)
CCA MRID 48139301	Adult Female 12 hr diet (6 pm-6 am)	RBC	0.66	0.55	1.03 (8 hr after feeding; 20 hr after food introduction)	0.6 (8 hr after feeding; 20 hr after food introduction)

[a] The homogeneous variance resulted in a lower BMDL than the model variance model and also provided an acceptable p value..
[b] An acceptable p value was not achieved.
[c] No computation (technical issues e.g., no convergence).

For exposure scenarios longer than acute duration, several high quality oral studies were available for BMD analyses and determination of oral PoDs for short- and intermediate-term incidental oral and chronic dietary scenarios. These included the new CCA study (MRID 48139301) in the rat, a developmental neurotoxicity rat study (MRID 44556901) and a special ChE study in the rat (MRID 44648101).

Table 3. Results of BMD Modeling of Pup Rat Brain and RBC ChE Inhibition following Repeat Oral Doses of Chlorpyrifos

Dataset	Sex/time of dosing	Endpoint/Route	BMD Program			
			R-based Program		EPA BMDS V2.1	
			BMD_{10}	$BMDL_{10}$	BMD_{10}	$BMDL_{10}$
CCA MRID 48139301)	PND 11-25 F (11 days) Gavage corn oil	Brain	0.60	0.48	0.80[a]	0.69[a]
CCA MRID 48139301)	PND 11-25 F (11 days) Gavage corn oil	RBC	0.17	0.15	0.17	0.15
CCA MRID 48139301)	PND 11-25 M (11 days) Gavage corn oil	Brain	0.32	0.3	0.63	0.52
CCA MRID 48139301)	PND 11-25 M (11 days) Gavage corn oil	RBC	0.077	0.04	0.11	0.09

[a] An acceptable p value was not achieved with BMDS program, however, there was good visual fit and value was similar to R-based program.

Table 4. Results of BMD Modeling of Adult Rat Brain, RBC and Heart ChE Inhibition following Repeat Oral Doses of Chlorpyrifos

Dataset	Sex/Time of Dosing	Endpoint/ Route	BMD Program/Software			
			R-based Program		EPA BMDS V2.1	
			BMD_{10}	$BMDL_{10}$	BMD_{10}	$BMDL_{10}$
Dow (Hoberman *et al.* 1998a,b MRID 44556901); Maurissen, 2000	Dams, GD6-20	Brain	0.65	0.51	0.65[a]	0.54[a]
Dow (Hoberman *et al.* 1998a,b MRID 44556901); Maurissen, 2000	Dams, GD6-20	RBC	0.06	0.04	0.06[a]	0.03[a]
Dow (Mattsson *et al.* 1998 44648101): Mattson, 2000	Dams, GD6-20	Brain	Hindbrain 1.1 Forebrain (no computation)[b]	Hindbrain 0.8 Forebrain (no computation)[b]	Hindbrain 1.1 Forebrain 1.2	Hindbrain 0.8 Forebrain 0.98
Dow (Mattsson *et al.* 1998 44648101): Mattson, 2000	Dams, GD6-20	RBC/ Heart	RBC 0.14 Heart 0.30	RBC 0.08 Heart 0.26	RBC 0.14[a] Heart 0.85[c]	RBC 0.08[a] Heart 0.22[c]
Dow (Mattsson *et al.* 1998 44648101): Mattson, 2000	Dams, LD1	Brain	Hindbrain 1.45 Forebrain (no computation)	Hindbrain 0.54 Forebrain (no computation)	Hindbrain 1.33 Forebrain 1.13	Hindbrain 0.65 Forebrain 0.89
Dow (Mattsson *et al.* 1998 44648101): Mattson, 2000	Dams, LD1	RBC	RBC 0.055 Heart 0.23	RBC 0.045 Heart 0.21	RBC 0.050 Heart 0.21	RBC 0.044 Heart 0.18
CCA MRID 48139301)	Adult F (11 days) Gavage corn oil	Brain	(no computation)	(no computation)	1.03 (8 hr)	0.95 (8 hr)
CCA MRID 48139301)	Adult F (11 days) Gavage corn oil	RBC	0.45	0.35	0.45[d]	0.35[d]

[a] The homogeneous variance provided a BMDL value and an acceptable p value.
[b] No computation (technical issues e.g., no convergence).
[c] An acceptable p value was not achieved with BMDS program. Submodel 5 had best AIC and a $BMDL_{10}$ value comparable to R-based program. Submodel 3 had BMD_{10} and $BMDL_{10}$ values similar to R-based runs but not the best AIC value.
[d] An acceptable p value was not achieved with BMDS program, however visual fits were good and values same as R-based program.

Table 5. CCA Acute BMD_{10} /$BMDL_{10}$ results for Chlorpyrifos Oxon: pup rats

	Male	Female
Chlorpyrifos oxon BMD_{10}/$BMDL_{10}$	Brain: 1.06/0.36 RBC: 0.093/0.050	Brain: No reliable fit[a] RBC: 0.081/0.063

[a]No reliable fit with BMDS program and no convergence in R-based program.

Table 6. CCA Acute BMD_{10} /$BMDL_{10}$ results for Chlorpyrifos Oxon: adult rats

	Male	Female
Chlorpyrifos oxon BMD_{10}/$BMDL_{10}$	Brain and RBC: Not examined	Brain; 1.66/0.80[a] RBC: 0.214/0.150

[a]BMD value from r-based program. Submodels 4 and 5 of the BMDS program failed to compute values

Table 7. CCA Chronic (11 day) BMD_{10} /$BMDL_{10}$ results for Chlorpyrifos Oxon: pup rats

	Male	Female
Chlorpyrifos oxon BMD_{10}/$BMDL_{10}$	Brain: No reliable fit[a] RBC: 0.029/0.024	Brain: 0.60/0.13 RBC: 0.027/0.025

[a]No convergence in r-based program. Bad completion or failure to compute BMD value in BMDS submodels 4 and 5.
[b]No acceptable P value with BMDS but good visual fit and comparable to value obtained with R-based program.

Table 8. CCA Chronic (11 day) BMD_{10}/$BMDL_{10}$ for Chlorpyrifos Oxon:adult rats

	Male	Female
Chlorpyrifos oxon BMD_{10}/$BMDL_{10}$	Brain and RBC: Not examined	Brain: No reliable fit [b] RBC: 0.025/0.011 (p=0.08)

[a]No acceptable P value not achieved in BMDS but good visual fit and same value as R-based program.
[b]No convergence in r-based program. Failure to compute BMD value in BMDS submodels 4 and 5.