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Part IV

## Environmental Protection Agency

40 CFR Part 180
Chlorpyrifos; Tolerance Revocations; Proposed Rule

## ENVIRONMENTAL PROTECTION AGENCY

### 40 CFR Part 180

**[EPA–HQ–OPP–2015–0653; FRL–9935–92]**

## Chlorpyrifos; Tolerance Revocations

**AGENCY:** Environmental Protection Agency (EPA).

**ACTION:** Proposed rule.

**SUMMARY:** On August 10, 2015, the U.S. Court of Appeals for the Ninth Circuit ordered EPA to respond to an administrative Petition to revoke all tolerances for the insecticide chlorpyrifos by October 31, 2015, by either denying the Petition or issuing a proposed or final tolerance revocation. At this time, the agency is unable to conclude that the risk from aggregate exposure from the use of chlorpyrifos meets the safety standard of section 408(b)(2) of the Federal Food, Drug, and Cosmetic Act (FFDCA). Accordingly, EPA is proposing to revoke all tolerances for chlorpyrifos. EPA is specifically soliciting comment on whether there is an interest in retaining any individual tolerances, or group of tolerances, and whether information exists to demonstrate that such tolerance(s) meet(s) the FFDCA section 408(b) safety standard. EPA encourages interested parties to comment on the tolerance revocations proposed in this document and on the proposed time frame for tolerance revocation. Issues not raised during the comment period may not be raised as objections to the final rule, or in any other challenge to the final rule.

**DATES:** Comments must be received on or before January 5, 2016.

**ADDRESSES:** Submit your comments, identified by docket identification (ID) number EPA–HQ–OPP–2015–0653 by one of the following methods:

- *Federal eRulemaking Portal: http://www.regulations.gov.* Follow the online instructions for submitting comments. Do not submit electronically any information you consider to be Confidential Business Information (CBI) or other information whose disclosure is restricted by statute.
- *Mail:* OPP Docket, Environmental Protection Agency Docket Center (EPA/DC), (28221T), 1200 Pennsylvania Ave. NW., Washington, DC 20460–0001.
- *Hand Delivery:* To make special arrangements for hand delivery or delivery of boxed information, please follow the instructions at *http://www.epa.gov/dockets/contacts.html.*

Additional instructions on commenting or visiting the docket, along with more information about dockets generally, is available at *http://www.epa.gov/dockets.*

**FOR FURTHER INFORMATION CONTACT:** Dana Friedman, Pesticide Re-Evaluation Division (7508P), Office of Pesticide Programs, Environmental Protection Agency, 1200 Pennsylvania Ave NW., Washington, DC 20460–0001; telephone number: (703) 347–8827; email address: *friedman.dana@epa.gov.*

**SUPPLEMENTARY INFORMATION:**

### I. General Information

*A. Does this action apply to me?*

You may be potentially affected by this action if you are an agricultural producer, food manufacturer, or pesticide manufacturer. The following list of North American Industrial Classification System (NAICS) codes is not intended to be exhaustive, but rather provides a guide to help readers determine whether this document applies to them. Potentially affected entities may include:

- Crop production (NAICS code 111).
- Animal production (NAICS code 112).
- Food manufacturing (NAICS code 311).
- Pesticide manufacturing (NAICS code 32532).

*B. What should I consider as I prepare my comments for EPA?*

1. *Submitting CBI.* Do not submit this information to EPA through regulations.gov or email. Clearly mark the part or all of the information that you claim to be CBI. For CBI information in a disk or CD–ROM that you mail to EPA, mark the outside of the disk or CD–ROM as CBI and then identify electronically within the disk or CD–ROM the specific information that is claimed as CBI. In addition to one complete version of the comment that includes information claimed as CBI, a copy of the comment that does not contain the information claimed as CBI must be submitted for inclusion in the public docket. Information so marked will not be disclosed except in accordance with procedures set forth in 40 CFR part 2.

2. *Tips for preparing your comments.* When preparing and submitting your comments, see the commenting tips at *http://www.epa.gov/dockets/comments.html.*

*C. What can I do if I wish the Agency to maintain a tolerance that the Agency proposes to revoke?*

This proposed rule provides a comment period of 60 days for any interested person to submit comments on the agency's proposal. EPA will issue a final rule after considering the comments that are submitted. Comments should be limited only to the pesticide and tolerances subject to this proposal.

EPA's finding that it cannot determine if aggregate exposure from all existing uses of chlorpyrifos are safe, does not necessarily mean that no individual tolerance or group of tolerances could meet the FFDCA 408(b)(2) safety standard and be maintained. EPA's risk assessment supporting this proposed rule indicates that the primary source of risk comes from chlorpyrifos and chlorpyrifos oxon in drinking water in highly vulnerable watersheds (generally small watersheds where the land is agricultural and could be treated with chlorpyrifos (*i.e.,* heavily cropped areas)). However, as explained in this proposed rule, some uses of chlorpyrifos do not by themselves present risks of concern from either food or drinking water and are only a concern when aggregated with all exposures to chlorpyrifos. EPA therefore invites comments that address whether some tolerances or groups of tolerances can be retained. In that regard, in addition to information related to the safety of such tolerances, use site specific information pertaining to the pests targeted by chlorpyrifos, and the alternatives to chlorpyrifos for these pests, may help to inform the agency's final decision if EPA is able to conclude that some tolerances may be retained under the FFDCA safety standard. In addition, if EPA receives information that would allow it to better refine the location of at risk watersheds and protect such watersheds through appropriate product labeling restrictions, it is possible EPA could conclude that such mitigation would eliminate the need for some or all of the proposed tolerance revocations. It is important to stress, however, that because the FFDCA is a safety standard, EPA can only retain chlorpyrifos tolerances if it is able to conclude that such tolerances are safe.

After consideration of comments, EPA will issue a final regulation determining whether revocation of some or all of the tolerances is appropriate under section 408(b)(2). Such regulation will be subject to objections pursuant to section 408(g) (21 U.S.C. 346a(g)) and 40 CFR part 178.

In addition to submitting comments in response to this proposal, you may also submit an objection at the time of the final rule. If you anticipate that you may wish to file objections to the final rule, you must raise those issues in your comments on this proposal. EPA received numerous comments on its

December 2014 Revised Human Health Risk Assessment (RHHRA) (Ref. 1) related to the scientific bases underlying this proposed rule. In light of the U.S Court of Appeals for the Ninth Circuit's August 10, 2015 order in *Pesticide Action Network North America (PANNA)* v. *EPA,* No. 14–72794 (*PANNA*), compelling EPA to take this action by October 31, 2015, EPA has not addressed these prior comments in this proposed rule. Persons wishing to have EPA consider previously submitted comments on the RHHRA in connection with this proposal should submit a comment indicating that intention and identifying their earlier comments on the RHHRA. EPA will treat as waived any issue not raised or referenced in comments submitted on this proposal. Similarly, if you fail to file an objection to the final rule within the time period specified, you will have waived the right to raise any issues resolved in the final rule. After the specified time, issues resolved in the final rule cannot be raised again in any subsequent proceedings on this rule making.

## II. Background

### *A. What action is the Agency taking?*

EPA is proposing to revoke all tolerances for residues of the insecticide chlorpyrifos as contained in 40 CFR 180.342. This includes tolerances for residues of chlorpyrifos on specific food commodities (180.342(a)(1)); on all food commodities treated in food handling and food service establishments in accordance with prescribed conditions (180.342(a)(2) and(a)(3)); and on specific commodities when used under regional registrations (180.342(c)).

The agency is proposing to revoke all of these tolerances because EPA cannot, at this time, determine that aggregate exposure to residues of chlorpyrifos, including all anticipated dietary exposures and all other non-occupational exposures for which there is reliable information, are safe.

EPA's full risk conclusions supporting this proposal are set forth in the 2014 RHHRA for chlorpyrifos that EPA issued for public comment. That document, supporting materials, and the public comments on those documents are available in the chlorpyrifos registration review docket, EPA–HQ–OPP–2008–0850. While EPA's assessment indicates that contributions to dietary exposures to chlorpyrifos from food and residential exposures are safe, when those exposures are combined with estimated exposures from drinking water, as required by the FFDCA, EPA has determined that safe levels of chlorpyrifos in the diet may be exceeded for people whose drinking water is derived from certain vulnerable watersheds throughout the United States. This primarily includes those populations consuming drinking water from small water systems in heavily cropped areas where chlorpyrifos may be used widely.

### *B. What is the Agency's authority for taking this action?*

EPA is taking this action, pursuant to the authority in FFDCA sections 408(b)(1)(A), 408(b)(2)(A), and 408(d)(4)(A)(ii). 21 U.S.C. 346a(b)(1)(A), (b)(2)(A), (d)(4)(A)(ii).

## III. Statutory and Regulatory Background

A ''tolerance'' represents the maximum level for residues of pesticide chemicals legally allowed in or on raw agricultural commodities and processed foods. Section 408 of FFDCA, 21 U.S.C. 346a, authorizes the establishment of tolerances, exemptions from tolerance requirements, modifications of tolerances, and revocation of tolerances for residues of pesticide chemicals in or on raw agricultural commodities and processed foods. Without a tolerance or exemption, food containing pesticide residues is considered to be unsafe and therefore ''adulterated'' under FFDCA section 402(a), 21 U.S.C. 342(a). Such food may not be distributed in interstate commerce, 21 U.S.C. 331(a). For a food-use pesticide to be sold and distributed, the pesticide must not only have appropriate tolerances under the FFDCA, but also must be registered under FIFRA, 7 U.S.C. 136a(a); 40 CFR 152.112(g). Food-use pesticides not registered in the United States must have tolerances in order for commodities treated with those pesticides to be imported into the United States.

Section 408(d) of the FFDCA, 21 U.S.C. 346a(d), authorizes EPA to revoke tolerances in response to administrative petitions submitted by any person. Because EPA is unable to determine at this time that aggregate exposures to chlorpyrifos are safe, EPA is proposing to revoke these tolerances in response to a Petition from PANNA and the Natural Resources Defense Council (NRDC) to revoke all chlorpyrifos tolerances (Ref. 2). The timing of this proposal is the result of the August 10, 2015 order in the PANNA decision to respond to that petition by October 31, 2015. This proposal also implements the agency findings made during the registration review process required by section 3(g) of FIFRA (7 U.S.C. 136(a)(g)) which EPA is conducting in parallel with its petition response. That process requires EPA to re-evaluate existing pesticides every 15 years to determine whether such pesticides meet the FIFRA registration standard set forth in FIFRA section 3(c)(5), 7 U.S.C. 136a(c)(5). In part, that standard requires EPA to ensure that dietary risks from the pesticide meet the FFDCA section 408 safety standard. Section 408 directs that EPA may establish or leave in effect a tolerance for pesticide only if it finds that the tolerance is safe, and EPA must revoke or modify tolerances determined to be unsafe. FFDCA 408(b)(2)(A)(i) (21 U.S.C. 346a(b)(2)(A)(i)). Section 408(b)(2)(A)(ii) defines ''safe'' to mean that ''there is a reasonable certainty that no harm will result from aggregate exposure to the pesticide chemical residue, including all anticipated dietary exposures and all other exposures for which there is reliable information.'' This includes exposure through drinking water and all non-occupational exposures (*e.g.* in residential settings), but does not include occupational exposures to workers (*i.e.,* occupational).

Risks to infants and children are given special consideration. Specifically, pursuant to section 408(b)(2)(C), EPA must assess the risk of the pesticide chemical based on available information concerning the special susceptibility of infants and children to the pesticide chemical residues, including neurological differences between infants and children and adults, and effects of in utero exposure to pesticide chemicals; and available information concerning the cumulative effects on infants and children of such residues and other substances that have a common mechanism of toxicity.

(21 U.S.C. 346a(b)(2)(C)(i)(II) and (III)).

This provision further directs that ''in the case of threshold effects, . . . an additional tenfold margin of safety for the pesticide chemical residue and other sources of exposure shall be applied for infants and children to take into account potential pre- and post-natal toxicity and completeness of the data with respect to exposure and toxicity to infants and children.'' (21 U.S.C. 346a(b)(2)(C)). EPA is permitted to ''use a different margin of safety for the pesticide chemical residue only if, on the basis of reliable data, such margin will be safe for infants and children.'' (21 U.S.C. 346a(b)(2)(C)). Due to Congress's focus on both pre- and post-natal toxicity, EPA has interpreted this additional safety factor as pertaining to risks to infants and children that arise due to pre-natal exposure as well as to exposure during childhood years. For

convenience sake, the legal requirements regarding the additional safety margin for infants and children in section 408(b)(2)(C) are referred to throughout this proposed rule as the ''FQPA safety factor for the protection of infants and children'' or simply the ''FQPA safety factor.''

## IV. Chlorpyrifos Background, Regulatory History, and Litigation

Chlorpyrifos (0,0-diethyl-0-3,5,6-trichloro-2-pyridyl phosphorothioate) is a broad-spectrum, chlorinated organophosphate (OP) insecticide that has been registered for use in the United States since 1965. Currently registered use sites include a large variety of food crops (including fruit and nut trees, many types of fruits and vegetables, and grain crops), and non-food use settings (*e.g.,* golf course turf, industrial sites, greenhouse and nursery production, sod farms, and wood products). Public health uses include aerial and ground-based fogger mosquito adulticide treatments, roach bait products and individual fire ant mound treatments. In 2000, the chlorpyrifos registrants reached an agreement with EPA to voluntarily cancel all residential use products except those registered for ant and roach baits in child-resistant packaging and fire ant mound treatments.

In 2006, EPA completed FIFRA section 4 reregistration and FFDCA tolerance reassessment for chlorpyrifos and the OP class of pesticides. Given ongoing scientific developments in the study of the OPs generally, EPA chose to prioritize the FIFRA section 3(g) registration review (the next round of re-evaluation following reregistration) of chlorpyrifos and the OP class. The registration review of chlorpyrifos and the OPs has presented EPA with numerous novel scientific issues that have been the subject of multiple FIFRA Scientific Advisory Panel (SAP) meetings since the completion of reregistration that have resulted in significant developments in the conduct of EPA's risk assessments generally, and, more specifically, in the study of chlorpyrifos's effects. These SAP meetings included review of new worker and non-occupational exposure methods, experimental toxicology and epidemiology, risk assessment approaches for semi-volatile pesticides and the evaluation of a chlorpyrifos-specific pharmacokinetic-pharmacodynamic (PBPK–PD) model.

### *A. Registration Review*

In 2011, in connection with FIFRA registration review, EPA issued its Preliminary Human Health Risk Assessment (PHHRA) (Ref. 3) for chlorpyrifos that evaluated exposures from food, drinking water, other non-occupational sources, and occupational risk (such as risks to farmworkers applying chlorpyrifos and working in treated fields). At the time of the PHHRA, EPA had not yet performed an integrated weight of evidence analysis on the lines of evidence related to the potential for neurodevelopmental effects. The PHHRA indicated that for food alone, the acute and chronic dietary risk estimates for all populations assessed were below the level of concern. The residue of concern in treated drinking water is the chlorpyrifos oxon because chlorpyrifos transforms to the more toxic chlorpyrifos oxon in treated drinking water (*e.g.* chlorination). For drinking water alone, EPA had a concern for infant exposures to the chlorpyrifos oxon.

In December 2014, EPA completed the RHHRA for registration review (Ref. 1). The RHHRA represents a highly sophisticated assessment of hazard and exposure to chlorpyrifos and its oxon. The dietary risk assessment in the RHHRA provides the scientific support for this proposed rule. The approach EPA used for the chlorpyrifos dietary assessment and for this proposed rule can be described as follows: EPA conducted dietary exposure modeling using the Dietary Exposure Evaluation Model (DEEM) and the Calendex models (Ref. 4) to develop a probabilistic evaluation of human dietary consumption. Most of the pesticide food residue values used in those models were based upon U.S. Department of Agriculture's (USDA) Pesticide Data Program (PDP) monitoring data. Percent crop treated and empirical food processing factors were used where available. EPA then utilized a PBPK–PD model to calculate both acute (24 hour) and steady state (21 days (*i.e.,* the approximate time to reach steady state for most OPs)) points of departure (PoD) dose levels that represent the minimum amount of chlorpyrifos that presents a risk concern. (OPs exhibit a phenomenon known as steady state AChE inhibition. After repeated dosing at the same dose level, the degree of inhibition comes into equilibrium with the production of new, uninhibited enzyme. OP AChE studies of 2–3 weeks generally show the same degree of inhibition as those of longer duration (*i.e.,* up to 2 years of exposure). Therefore, a steady state assessment based on 21 days of exposure may be conducted in place of the traditional chronic assessment).

For chlorpyrifos, the risk of concern is 10% acetylcholinesterase inhibition (AChE) in red blood cells (RBC)—a precursor for adverse neurological symptoms—for both acute and steady state exposure durations. The PBPK–PD PoD predictions for each human lifestage exposure route and pathway were modeled separately (*e.g.,* for residential exposure *i.e.* dermal, inhalation and incidental oral calculations). PoDs are divided by the total uncertainty factors (which are used to account for potential differences in sensitivities within populations or extrapolations from test results in animals to effects on humans) to derive a population adjusted dose (PAD). There are potential risks of concern when the estimated dietary exposures exceed 100% of the PAD. For the food intake portion of the dietary assessment, the only potential residue of concern is chlorpyrifos (the oxon metabolite is not an expected residue on foods). EPA incorporated total uncertainty factors of 100X for adult females (a 10X FQPA safety factor and another 10X intra-species extrapolation factor since the PBPK–PD model does not include a component that specifically models pregnant women) and 40X for the other relevant populations (a 10X FQPA safety factor and another 4X intra-species data derived extrapolation factor) using the PBPK–PD model to account for potential metabolic and physiological differences between populations. The chlorpyrifos exposure values resulting from dietary modeling are then compared to the PAD to determine the portion of the ''risk cup'' that is taken up by exposures from food. In the case of chlorpyrifos, the RHHRA concluded that food and non-occupational exposures by themselves take up only a small portion of the risk cup and are therefore not a risk concern when considered in isolation.

For the drinking water portion of the dietary assessment, the chlorpyrifos oxon, which is more toxic than chlorpyrifos, is the residue of concern assumed to occur in drinking water. Based on available information regarding the potential effects of certain water treatments (*e.g.,* chlorination appears to hasten transformation of chlorpyrifos to chlorpyrifos oxon), EPA believes it is appropriate to assume that all chlorpyrifos in water is converted to chlorpyrifos oxon upon treatment. The chlorpyrifos oxon total uncertainty factors are 100X for adult females (10X FQPA safety factor and 10X intra-species extrapolation factor to account for potential differences between populations) and 50X for the other

relevant populations (10X FQPA safety factor and 5X intra-species data derived extrapolation factor) using the PBPK–PD model to account for potential metabolic and physiological differences between populations. See Unit VI.5 for how the intra-species factors for chlorpyrifos and chlorpyrifos oxon were derived. After considering food and residential contributions to the risk cup, EPA determined that drinking water concentrations to chlorpyrifos oxon greater than 3.9 ppb for a 21-day average would exceed EPA's Drinking Water Level of Comparison (DWLOC) and present a risk of concern. EPA's water exposure assessment indicated that multiple labeled use scenarios for chlorpyrifos exceed the DWLOC and therefore present a risk concern. On January 14 2015, EPA published a **Federal Register** Notice seeking public comment on the RHHRA.

EPA's drinking water analysis in the RHHRA also showed that the DWLOC exceedances are not expected to be uniformly distributed across the country. As a result, EPA began to conduct further analysis to look at the spatial distribution of Estimated Drinking Water Concentrations (EDWCs) at more refined geographic levels. This exercise demonstrated that chlorpyrifos applications will result in variable drinking water exposures that are highly localized and that the highest exposures generally occur in small watersheds where there is a high percent cropped area on which chlorpyrifos use could occur. Accordingly, following the development of the RHHRA in December 2014, EPA has continued working to develop a more refined assessment to examine EDWCs on a regional and/or watershed scale to pinpoint community drinking water systems where exposure to chlorpyrifos oxon as a result of chlorpyrifos applications may pose an exposure concern. At this time this more refined drinking water assessment that will allow EPA to better identify where at-risk watersheds are located throughout the country is not completed. Thus, we are not currently able to determine with any great specificity which uses in which areas of the country do or do not present a risk concern. EPA intends to update this action, as warranted, with any significant refinements to its drinking water assessment, and intends, to the extent practicable, to provide the public an opportunity to comment on the refined drinking water assessment prior to a final rule.

### *B. PANNA±NRDC Petition and Associated Litigation*

In September 2007, PANNA and NRDC submitted to EPA a Petition seeking revocation of all chlorpyrifos tolerances and cancellation of all FIFRA registrations of products containing chlorpyrifos. In connection with both EPA's response to the Petition and the FIFRA registration review of chlorpyrifos, EPA has taken most of the complex and novel science questions raised in the Petition to the SAP for review and EPA has developed numerous new methodologies (including approaches to address pesticide drift, volatility, and the integration of experimental toxicology and epidemiology) to consider these issues.

While EPA agreed that these new methodologies were necessary to properly evaluate PANNA and NRDC's (Petitioners') claims, Petitioners have been dissatisfied with the pace of EPA's response efforts and have sued EPA in federal court on three separate occasions to compel a prompt response to the Petition. Although EPA has to date addressed 7 of the 10 claims asserted in the Petition by either issuing a preliminary denial or approving label mitigation to address the claim, on June 10, 2015, in the *PANNA* decision, the U.S. Court of Appeals for the Ninth Circuit signaled its intent to order EPA to complete its response to the Petition and directed EPA to inform the court how—and by when—EPA intended to respond. On June 30, 2015, EPA informed the court that, based on the results of its drinking water assessment, EPA intended to propose by April 15, 2016, the revocation of all chlorpyrifos tolerances in the absence of pesticide label mitigation that ensures that drinking water exposures will be safe. EPA proposed this time frame in part to accommodate the completion of a refined drinking water assessment that might allow EPA to identify high risk areas of the country where additional label mitigation could be put in place to address drinking water concerns. On August 10, 2015, the court rejected EPA's time line and issued a mandamus order directing EPA to ''issue either a proposed or final revocation rule or a full and final response to the administrative Petition by October 31, 2015.'' As a result of this order, EPA is issuing this proposed rule in advance of completing its refined drinking water assessment. In addition, EPA has had insufficient time to address comments received on the RHHRA. As a result, EPA may update this action with new or modified analyses as EPA completes additional work after this proposal. For any significant new or modified analyses, to the extent practicable, EPA intends to provide the public an opportunity to comment on that work prior to issuing a final rule.

## V. EPA's Approach to Dietary Risk Assessment

EPA performs a number of analyses to determine the risks from aggregate exposure to pesticide residues. A short summary is provided below to aid the reader. For further discussion of the regulatory requirements of section 408 of the FFDCA and a complete description of the risk assessment process, refer to References 5 and 6 respectively. To assess the risk of a pesticide tolerance, EPA combines information on pesticide toxicity with information regarding the route, magnitude, and duration of exposure to the pesticide. The risk assessment process involves four distinct steps: (1) Identification of the toxicological hazards posed by a pesticide; (2) determination of the exposure ''level of concern'' for humans; (3) estimation of human exposure; and (4) characterization of human risk based on comparison of human exposure to the level of concern.

### *A. Hazard Identification and Selection of Toxicological Endpoint*

Any risk assessment begins with an evaluation of a chemical's inherent properties, and whether those properties have the potential to cause adverse effects (*i.e.,* a hazard identification). EPA then evaluates the hazards to determine the most sensitive and appropriate adverse effect of concern, based on factors such as the effect's relevance to humans and the likely routes of exposure.

Once a pesticide's potential hazards are identified, EPA determines a toxicological level of concern for evaluating the risk posed by human exposure to the pesticide. In this step of the risk assessment process, EPA essentially evaluates the levels of exposure to the pesticide at which effects might occur. An important aspect of this determination is assessing the relationship between exposure (dose) and response (often referred to as the dose-response analysis). In evaluating a chemical's dietary risks, EPA uses a reference dose (RfD) approach, which first involves establishing a PoD—or the value from a dose-response curve that is at the low end of the observable data and that is the toxic dose that serves as the starting point in extrapolating a risk to the human population. In typical risk assessments, PoDs are derived directly

from laboratory animal studies, and then EPA extrapolates to potential effects on humans and human populations by applying both inter and intra-species uncertainty factors. Traditionally, EPA has used a 10X factor to address each of these uncertainties. In the case of chlorpyrifos and its oxon, however, EPA has used PBPK–PD modeling to estimate PoDs for all age groups using Data-Derived Extrapolation Factors (DDEF) rather than default uncertainty factors to address intraspecies extrapolation for some groups (Ref. 1). The PBPK–PD model accounts for PK (pharmacokinetic) and PD (pharmacodynamic) characteristics to derive age, duration, and route specific PoDs. Specifically, the following characteristics have been evaluated: exposure (acute, 21-day (steady state); routes of exposure (dermal, oral, inhalation); body weights which vary by lifestage; exposure duration (hours per day, days per week); and exposure frequency (*e.g.,* eating and drinking events per day). While the current PBPK–PD model accounts for age-related growth from infancy to adulthood by using polynomial equations to describe tissue volumes and blood flows as a function of age, the model does not include any descriptions on physiological, anatomical, and biochemical changes associated with pregnancy. Due to the uncertainty in extrapolating the current model predictions among women who may be pregnant, the agency is applying the standard 10X intra-species extrapolation factor for women of childbearing age.

Although the PBPK–PD model's use of data-derived extrapolation factors renders unnecessary the use of traditional inter- and intra- species uncertainty factors for evaluating most populations, as required by FFDCA section 408(b)(2)(C), EPA must also address the need for an additional safety factor to protect infants and children. That provision requires EPA to retain an additional 10-fold margin of safety unless EPA concludes, based on reliable data, that a different safety factor will be safe for infants and children. The PoDs calculated by the PBPK–PD model are then divided by the uncertainty factors to derive a PAD. There are potential risks of concern when the estimated dietary exposure exceeds 100% of the PAD.

*B. Estimating Human Exposure Levels*

Pursuant to section 408(b) of the FFDCA, EPA evaluated dietary risks for chlorpyrifos based on ''aggregate exposure'' to chlorpyrifos. By ''aggregate exposure,'' EPA is referring to exposure to chlorpyrifos residues by multiple pathways of exposure. EPA uses available data, together with assumptions designed to be protective of public health, and standard analytical methods to produce separate estimates of exposure for a highly exposed subgroup of the general population, for each potential pathway and route of exposure. For both acute and steady state risks, EPA then calculates potential aggregate exposure and risk by using probabilistic techniques to combine distributions of potential exposures in the population for each route or pathway. (Probabilistic analysis is used to predict the frequency with which variations of a given event will occur. By taking into account the actual distribution of possible consumption and pesticide residue values, probabilistic analysis for pesticide exposure assessments ''provides more accurate information on the range and probability of possible exposure and their associated risk values.'' (Ref. 7). In capsule, a probabilistic pesticide exposure analysis constructs a distribution of potential exposures based on data on consumption patterns and residue levels and provides a ranking of the probability that each potential exposure will occur. People consume differing amounts of the same foods, including none at all, and a food will contain differing amounts of a pesticide residue, including none at all). For dietary analyses, the relevant sources of potential exposure to chlorpyrifos are from the ingestion of residues in food and drinking water. EPA uses a combination of monitoring data and predictive models to evaluate environmental exposure of humans to chlorpyrifos.

1. *Exposure from food.* Acute and steady state dietary (food only) exposure analyses for chlorpyrifos were conducted using the Dietary Exposure Evaluation Model (DEEM) and Calendex software with the Food Commodity Intake Database (FCID). The DEEM–FCID model uses 2003–2008 food consumption data from the USDA National Health and Nutrition Examination Survey, What We Eat in America (NHANES/WWEIA). These current analyses reflect the latest available consumption data as well as more recent food monitoring and percent crop treated data. Both the acute and steady state dietary exposure analyses are highly refined. The large majority of food residues used were based upon USDA's PDP monitoring data except in a few instances where no appropriate PDP data were available. In those cases, field trial data or tolerance level residues were assumed.

DEEM–FCID also compares exposure estimates to appropriate RfD or PAD values to estimate risk. EPA uses these models to estimate exposure for the general U.S. population as well as subpopulations based on age, sex, ethnicity, and region. For its chlorpyrifos assessment, EPA used DEEM–FCID to calculate risk estimates based on a probabilistic distribution that combines the full range of residue values for each food with the full range of data on individual consumption amounts to create a distribution of exposure and risk levels. More specifically, DEEM–FCID creates this distribution by calculating an exposure value for each reported day of consumption per person (''person/day'') in the food survey, assuming that all foods potentially bearing the pesticide residue contain such residue at the chosen value. The exposure amounts for the thousands of person/days in the food survey are then collected in a frequency distribution.

The probabilistic technique that DEEM–FCID uses to combine differing levels of consumption and residues involves the following steps:

(1) identification of any food(s) that could possibly bear the residue in question for each person/day in the USDA food survey;

(2) calculation of an exposure level for each of the thousands of person/days in the USDA food survey database, based on the foods identified in Step #1 by randomly selecting residue values for the foods from the residue database;

(3) repetition of Step #2 one thousand times for each person/day; and

(4) collection of all of the hundreds of thousands of potential exposures estimated in Steps # 2 and 3 in a frequency distribution.

The resulting probabilistic assessment presents a range of exposure/risk estimates that can be compared to appropriate PADs to determine the safety of food exposures.

*2. Exposure from water.* EPA may use field monitoring data and/or simulation water exposure models to generate pesticide exposure estimates in drinking water. Monitoring and modeling are both important tools for estimating pesticide concentrations in water and can provide different types of information. Monitoring data can provide estimates of pesticide concentrations in water that are representative of the specific agricultural or residential pesticide practices in specific locations, under the environmental conditions associated with a sampling design (*i.e.,* the

locations of sampling, the times of the year samples were taken, and the frequency by which samples were collected). Further, monitoring data can reflect the actual use of a pesticide rather than the label rates. Although monitoring data can provide a direct measure of the concentration of a pesticide in water, it generally does not provide a reliable basis for estimating spatial and temporal variability in exposures because sampling may not occur in areas with the highest pesticide use, and/or when the pesticides are being used and/or at an appropriate sampling frequency to detect high concentrations of a pesticide that occur over the period of a day to several days.

Because of the limitations in most monitoring studies, EPA's standard approach is to use water exposure models as the primary means to estimate pesticide exposure levels in drinking water. EPA's computer models use detailed information on soil properties, crop characteristics, and weather patterns to estimate exposure in vulnerable locations where the pesticide could be used according to its label. (Ref. 8). These models calculate estimated water concentrations of pesticides using laboratory data that describe how fast the pesticide breaks down to other chemicals and how it moves in the environment at these vulnerable locations. The modeling provides an estimate of pesticide concentrations in ground and surface water. Depending on the modeling algorithm (*e.g.,* surface water modeling scenarios), daily concentrations can be estimated continuously over long periods of time, and for places that are of most interest for any particular pesticide.

As discussed in Unit VI.B. in greater detail, EPA relied on models developed for estimating exposure in both surface water and ground water. A detailed description of the models routinely used for exposure assessment is available from the EPA Office of Pesticide Programs (OPP) Water Models Web site: *http://www.epa.gov/oppefed1/models/water/.* The Surface Water Concentration Calculator provides a means for EPA to estimate daily pesticide concentrations in surface water sources of drinking water (a reservoir) using local soil, site, hydrology, and weather characteristics along with pesticide applications and agricultural management practices, and pesticide environmental fate and transport properties. EPA also considers percent cropped area (PCA) factors which take into account the potential extent of cropped areas that could be treated with pesticides in a particular area.

In modeling potential surface water concentrations, EPA attempts to model areas of the country that are highly vulnerable to surface water contamination rather than simply model ''typical'' concentrations occurring across the nation. Consequently, EPA models exposures occurring in small watersheds in different growing areas throughout the country over a 30-year period. The scenarios are designed to capture residue levels in vulnerable drinking water sources and are adjusted by PCA factors. The PCA is calculated from satellite derived land cover data to account for the area of watershed that is cropped.

EPA believes these assessments are likely reflective of a subset of the watersheds across the country that are used for drinking water supply, representing a drinking water source generally considered to be more vulnerable to frequent high concentrations of pesticides than most locations. For this reason, in its evaluation of chlorpyrifos, EPA has also begun to refine its assessment to evaluate drinking water risk at a regional and drinking water intake scale. While it is currently challenging to assess exposure on a local scale due to the unavailability of data and wide range of characteristics (*i.e.,* environmental factors such as soil, weather, etc. or others (*e.g.,* drinking water treatment process)) that affect the vulnerability of a given community drinking water system to chlorpyrifos oxon contamination, EPA developed a method to examine the potential geospatial concentration differences using specific examples for two Hydrological Unit Code (HUC) 2 Regions—HUC 2 Region 17: Pacific Northwest and HUC 2 Region 3: South Atlantic-Gulf, in order to identify use patterns in those regions that may result in EDWCs that exceed the DWLOC on a regional basis. There are 21 HUC 2 regions with 18 in the conterminous United States. These areas contain either the drainage area of a major river, or a combined drainage of a series of rivers. The average size is 177,560 square miles. Additional information can be found at *https://water.usgs.gov/GIS/huc.html.* The analysis used a number of modeling scenarios to represent all potential chlorpyrifos agricultural use sites. This analysis showed an overlap of potential chlorpyrifos use sites that may result in an exceedance of the DWLOC with watersheds that supply source water for community drinking water systems. In addition, this analysis shows that exposure is not uniform within a HUC 2 Region and that some watersheds present risk concerns while others do not. In general, the refined analysis confirms that smaller watersheds with high percent cropped areas are much more vulnerable than large watersheds. When this assessment is complete (*i.e.,* when EPA has completed this analysis for the rest of the country), it may provide EPA with a basis for tailoring its drinking water risk mitigation efforts through pesticide product labeling rather than revoking tolerances nationwide. Because of the *PANNA* decision on August 10, 2015 compelling EPA to respond to the PANNA–NRDC Petition by October 31, 2015, EPA has not been able to complete its refined drinking water assessment for chlorpyrifos in advance of this proposed rule. As a result, this proposal relies only on the results of the national screen that do not provide a basis for more tailored risk mitigation. EPA is continuing to conduct its regional and water-intake level assessment and intends to update this action if warranted with the results of that assessment when it is completed. For any significant new or modified drinking water analyses, to the extent practicable, EPA intends to provide the public an opportunity to comment on the work prior to issuing a final rule.

3. *Residential and Other Non-Occupational Exposures.* EPA's ''residential'' assessments actually examine exposure to pesticides in both residential and other non-occupational settings (*e.g.,* homes, parks, schools, athletic fields or any other areas frequented by the general public). All residential uses of chlorpyrifos except ant and roach baits (in child resistant packaging) and fire ant mound treatments were voluntary cancelled by registrants in 2000. As such, the use of the term ''residential'' throughout this document does not connote there are residential uses, rather it is used interchangeable with ''non-occupational'' exposures. Exposures to pesticides may occur to persons who apply pesticides or to persons who enter areas previously treated with pesticides. Such exposures may occur through oral, inhalation, or dermal routes. For chlorpyrifos, the uses that could result in non-occupational exposures are the public health uses as an aerial and ground-based ultra-low volume (ULV) fogger for adult mosquito control, the fire ant mound treatments, the use in ant and roach bait stations, and foliar use on golf course turfgrass.

Non-occupational assessments are conducted through examination of significant exposure scenarios (*e.g.,*

children playing on treated lawns or homeowners spraying their gardens) using a combination of generic and pesticide-specific data. To regularize this process, OPP has prepared Standard Operating Procedures (SOPs) for conducting ''residential'' assessments on a wide array of scenarios that are intended to address all major possible means by which individuals could be exposed to pesticides in a non-occupational environment (*e.g.* homes, schools, parks, athletic fields, or other publicly accessible locations). The SOPs identify relevant generic data and construct algorithms for calculating exposure amounts using these generic data in combination with pesticide-specific information. The generic data generally involve survey data on behavior patterns (*e.g.,* activities conducted on turf and time spent on these activities), unit exposure, and transfer coefficient data to evaluate the transfer of pesticide to humans from a treated surface.

Typically, non-occupational risks are quantified by comparison of estimates of exposure to toxicological PoDs for each route of exposure as selected from laboratory animal studies. In the case of chlorpyrifos, the PBPK–PD model was used to derive age-, duration-, and route-specific human equivalent doses. Separate PoDs were calculated for residential exposures by varying inputs on types of exposures and populations exposed. Residential risk estimates, or margins of exposure (MOEs) were calculated with use of the scenario- and lifestage-specific PoDs by comparison to exposure estimates (doses) quantified with use of standard occupational and residential exposure assessment methodologies.

### *C. Selection of Acute and Steady State Dietary Exposure Level of Concern*

Because probabilistic assessments generally present a realistic range of residue values to which the population may be exposed, EPA's starting point for estimating exposure and risk for its aggregate risk assessments is the 99.9th percentile of the population under evaluation. When using a probabilistic method of estimating acute and steady state dietary exposure, EPA typically assumes that, when the 99.9th percentile of exposure is equal to or less than the PAD, the level of concern has not been exceeded and dietary exposures are safe.

### *D. Aggregating Exposures and Deriving a Risk Estimate*

In an aggregate risk assessment, pesticide exposures from relevant sources (*i.e.,* food, drinking water and non-occupational uses) are added together and compared to quantitative estimates of hazard (*e.g.,* PAD), or the risks themselves can be aggregated. When aggregating exposures and risks from various sources, both the route and duration of exposures are considered. For chlorpyrifos, EPA has considered aggregate exposures and risks from combined food, drinking water, and non-occupational exposures. Residues in food consist of parent compound chlorpyrifos only, while concentrations in water are assumed to consist of chlorpyrifos oxon only. The acute aggregate assessment includes only food and drinking water while the steady state aggregate assessment includes exposures from food, drinking water, and non-occupational scenarios. Typically, in aggregate assessments, total dietary exposure (food and drinking water combined) are derived by incorporating both food residues and EDWCs in the dietary exposure model. In the chlorpyrifos RHHRA, only food exposures were derived from the dietary model. For drinking water exposure and risk, a DWLOC approach was used to calculate the amount of exposure which could occur without exceeding the risk level of concern (*i.e.,* the available space in the total aggregate risk cup for exposures to chlorpyrifos oxon in drinking water after accounting for exposures to parent chlorpyrifos from food and non-occupational scenarios). The calculated DWLOCs were then compared to the EDWCs of oxon modeled under a variety of conditions. When the EDWC is less than the DWLOC, there are no risk concerns for exposures to the pesticide in drinking water which also indicates aggregate exposures are not of concern. Conversely, when the EDWC is greater than the DWLOC, then potential risks of concern are identified.

## VI. Aggregate Risk Assessment and Conclusions Regarding Safety

Consistent with section 408(b)(2)(D) of FFDCA, EPA has reviewed the available scientific data and other relevant information in support of this action. EPA's assessment of exposures and risks associated with chlorpyrifos use follows.

### *A. Hazard Identification and Endpoint Selection*

This unit summarizes EPA's review of relevant data for extrapolating risk and its integrative analysis using multiple lines of evidence from experimental toxicology and epidemiology with respect to AChE/ChE inhibition (acetylcholinesterase/cholinesterase) and neurodevelopmental outcomes. This section also describes EPA's use of a robust PBPK–PD model for deriving PoDs and refined intra-species factors. Finally, this unit provides the quantitative results of the end-point selection process, including EPA's evaluation and application of the FQPA safety factor.

*1. Background.* Mode of action (MOA) and adverse outcome pathways (AOPs) provide important concepts and organizing tools for risk assessment. MOAs/AOPs describe a set of measureable key events that make up the biological processes leading to an adverse outcome and the causal linkages between such events. An AOP further defines the initial step in the process as the molecular initiating event. Fundamentally, MOA and AOP are different terms for basically the same concept.

It is well established that AChE inhibition is the mode of action/adverse outcome pathway (MOA/AOP) for the cholinergic toxicity of OP pesticides, including chlorpyrifos. AChE breaks down acetylcholine (ACh), a compound that assists in transmitting signals through the nervous system. When AChE is inhibited at nerve endings by chlorpyrifos or another AChE inhibiting pesticide, the inhibition prevents the ACh from being degraded and results in prolonged stimulation of nerves and muscles. If a person has enough exposure to chlorpyrifos for poisoning to occur the physical signs and symptoms include headache, nausea, dizziness, blurred vision, slurred speech, excessive perspiration, salivation, vomiting, diarrhea, and muscle twitching. Severe exposure to chlorpyrifos can lead to convulsions, loss of bladder and bowel control, coma, difficulty breathing, pulmonary edema, muscle paralysis, and death from respiratory failure. Because AChE inhibition is the initiating event for this MOA/AOP, using AChE inhibition as a regulatory endpoint is protective of downstream cholinergic effects. Moreover, given the sensitivity of AChE inhibition data for OPs, using AChE inhibition to establish a regulatory point of departure has historically been considered to be protective of other potential toxicities. EPA uses a value of 10% AChE inhibition as a point of departure in its regulation of AChE inhibiting pesticides, including chlorpyrifos. EPA's analyses have demonstrated that 10% is a level that can be reliably measured in the majority of animal toxicity studies; 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.

Newer lines of research on chlorpyrifos, notably epidemiological studies, have raised some uncertainty about EPA's historical risk assessment approach for chlorpyrifos with regard to the potential for neurodevelopmental effects that may arise from prenatal exposure to chlorpyrifos. This research is summarized in Unit VI.A.6.iii.

*2. Summary of data evaluated for deriving PoDs.* Chlorpyrifos and its oxon are widely studied and thus have an extensive database of scientific studies. Included in the database are: Studies developed by registrants pursuant to EPA guidelines, special studies conducted by the registrants, and studies in the public literature. These studies reflect different levels of biological organization (*e.g.,* metabolism, MOA/AOP, *in vitro* and *in vivo* experimental toxicology, biomonitoring, and epidemiology), various species (mouse, rabbit, dog, non-rodent, and human) and address multiple lifestages (fetal, postnatal, pregnant, and non-pregnant adult). The metabolism and pharmacokinetic (PK) profile of chlorpyrifos and its oxon have been extensively studied in *in vitro* systems, *in vivo* laboratory animals, as well as humans. Chlorpyrifos is bioactivated to the more toxic and potent AChE inhibitor, the oxon form. 3,5,6-trichloro-2-pyridinol (TCPy) is the major excreted metabolite and is used as the biomarker in PK, biomonitoring, and epidemiology studies. Diethylphosphate (DEP) is another metabolite often used in biomonitoring studies, but since it is produced by a number of OPs, DEP is not a specific marker for chlorpyrifos.

Summarized below are key findings from experimental toxicology studies on AChE inhibition as presented in detail in the June 2011 PHHRA and the December 2014 RHHRA. Readers should refer to those documents (Refs. 3 and 1) and their appendices in the public docket for this proposed rule for a complete summary of EPA's data review. Chlorpyrifos has also been evaluated for other adverse outcomes such as reproductive toxicity, developmental toxicity, cancer, genotoxicity, dermal toxicity, inhalation toxicity, and immunotoxicity. These adverse outcomes are less sensitive (*i.e.,* are likely to occur at higher doses) than AChE inhibition and neurodevelopmental effects, which form the scientific foundation of this proposed rule, and are thus not discussed in detail here. Concerns for neurodevelopmental effects provide the basis for retention of the FQPA safety factor and are summarized in Unit VI.A.6.

AChE inhibition remains the most robust quantitative dose response data for chlorpyrifos and thus continues to be the critical effect for the quantitative risk assessment. This approach is consistent with the advice EPA received from the FIFRA SAP in both 2008 and 2012 (Refs. 9 and 10) when EPA sought input specifically on the agency's approach to evaluating the toxicity of chlorpyrifos. EPA has conducted benchmark dose (BMD) analysis of numerous studies using empirical approaches previously endorsed by the FIFRA SAP (Ref. 11) and consistent with the 2006 OP cumulative risk assessment (Ref. 12) and other single chemical OP risk assessments. Details on AChE studies and related analyses can be found in Appendix 1 of the PHHRA (Ref. 3).

There are many chlorpyrifos studies evaluating AChE inhibition in red blood cell (RBC) or brain in multiple lifestages (gestational, fetal, post-natal, and non-pregnant adult), multiple species (rat, mouse, rabbit, dog, human), methods of oral administration (oral gavage with corn oil, dietary, gavage via milk), and routes of exposure (oral, dermal, inhalation via vapor, and via aerosol). In addition, chlorpyrifos is unique in the availability of ChE data from peripheral tissues in some studies (*e.g.,* heart, lung, liver). There are also literature studies comparing the *in vitro* ChE response to a variety of tissues (Ref. 13) which show similar sensitivity and intrinsic activity. Across the database, brain AChE tends to be less sensitive than RBC AChE or peripheral ChE. In oral studies, RBC AChE inhibition is generally similar in response to peripheral tissues (*e.g.,* liver, heart, and lung). Thus, the *in vitro* data and oral studies combined support the continued use of RBC AChE inhibition as the critical effect for quantitative dose-response assessment.

As with many OPs, female rats tend to be more sensitive than males to these AChE effects. For chlorpyrifos, there are data from multiple studies which provide robust RBC AChE data in pregnant, lactating, and non-pregnant female rats from oral exposure (*e.g.,* DNT, reproductive, and subchronic rats), respectively. The $BMD_{10}$/$BMDL_{10}$ values from these studies range from 0.05/0.04 to 0.15/0.09 mg/kg/day. ($BMD_{10}$ is the estimated dose to yield 10% inhibition in RBC AChE inhibition compared to controls or background levels. The $BMDL_{10}$ is the lower 95% confidence limit on the $BMD_{10}$). Studies are available in juvenile pups which show age-dependent differences, particularly following acute exposures, in sensitivity to chlorpyrifos and its oxon. As discussed above, this sensitivity is not derived from differences in the AChE enzyme itself but instead is derived largely from the immature metabolic clearance capacity in the juveniles.

Multiple route-specific laboratory animal studies for the dermal and inhalation routes are available. Dermal AChE data are available from a 21-day study and 4-day probe study (Ref. 14) in rats which together establish a No Observed Adverse Effect Level (NOAEL) of 5 mg/kg/day and a Lowest Observed Adverse Effect Level (LOAEL) of 10 mg/kg/day. Two subchronic inhalation toxicity studies (Refs. 15, 16, and 17) in the rat are available using vapor phase chlorpyrifos which show no ChE effects up to a concentration of 20.6 ppb (287 $\mu g/m^3$ or 0.082 mg/kg/day). Multiple acute inhalation studies are also available. In a special acute inhalation study, female rats were exposed by nose only (mass median aerodynamic diameter/geometric standard deviation was 1.9/1.51, respectively) 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 (Refs. 18 and 19). Consistent and significant lung 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 $\geq$ 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.

Since the 2011 PHHRA, two acute inhalation studies on the saturated vapor have been performed on the parent chlorpyrifos and chlorpyrifos oxon (Refs. 20 and 21). In these studies, female rats were exposed by nose only to a saturated vapor of chlorpyrifos or its oxon for 6 hours to a time-weighted concentration of 17.7 ppb (0.254 $mg/m^3$) (Ref. 20) or 2.58 ppb (35.3 $\mu g/m^3$) (Ref. 21), respectively. There were no statistically-significant decreases in ChE activity in the RBC, lung, brain, or plasma tissues. These acute studies along with the subchronic inhalation studies with vapor phase chlorpyrifos support a conclusion that acute exposure to the saturated vapor of chlorpyrifos or its oxon do not result in hazard due to AChE inhibition.

*3. Durations of Exposure, Critical Windows of Exposure, & Temporality of Effects Relevant for AChE Inhibition.* In risk assessment, exposure is evaluated in conjunction with the toxicology profile. More specifically, a variety of pharmacokinetic and pharmacodynamic factors are considered. In the case of

chlorpyrifos, exposure can occur from a single exposure (*e.g.,* eating a meal) or from repeated days of exposure (*e.g.,* worker, residential).

With respect to AChE inhibition, these effects can occur from a single exposure or from repeated exposures. Generally, for OPs, repeated exposures result in more AChE inhibition at a given administered dose compared to acute studies. Moreover, AChE inhibition in repeated dosing guideline toxicology studies with OPs show a consistent pattern of inhibition reaching steady state at or around 2–3 weeks of exposure in adult laboratory animals (Ref. 22). This pattern is observed with repeated dosing and is a result of an equilibrium between the amount of AChE inhibition and the production of new enzyme. As such, AChE studies of 2–3 weeks generally show the same degree of inhibition with those of longer duration (*i.e.,* up to 2 years of exposure). Thus, for most of the single chemical human health risk assessments for the OPs, EPA is focusing on the critical duration range from a single day up to 21 days (*i.e.,* the approximate time to reach steady state for most OPs). As described below, PoDs for various lifestages, routes, and scenarios have been derived at the acute and steady state durations. For this proposed rule, PoDs for various lifestages, routes, and scenarios have been derived at the acute and steady state durations.

*4. Use of the Chlorpyrifos PBPK±PD Model to Establish PoDs.* As described in detail in EPA's 2006 document entitled, ''Approaches for the Application of Physiologically Based Pharmacokinetic (PBPK) Models and Supporting Data in Risk Assessment,'' (Ref. 23) PBPK modelling is a scientifically sound and robust approach to estimating the internal dose of a chemical at a target site and as a means to evaluate and describe the uncertainty in risk assessments. PBPK models consist of a series of mathematical representations of biological tissues and physiological processes in the body that simulate the absorption, distribution, metabolism, and excretion (ADME) of chemicals that enter the body. Examples of PBPK model applications in risk assessments include interspecies extrapolation, intra-species extrapolation, route-to-route extrapolation, estimation of response from varying exposure conditions, and high-to-low dose extrapolation. PBPK models can be used in conjunction with an exposure assessment to improve the quantitative characterization of the dose-response relationship and the overall risk assessment. These models can also be used to evaluate the relationship between an applied dose and biomonitoring data.

For a full discussion of the development and evaluation of the chlorpyrifos PBPK–PD model, please refer to the December 2014 RHHRA (Ref. 1) in the public docket for this rule.

As discussed above, in typical risk assessments, PoDs are derived directly from laboratory animal studies and inter- and intra-species extrapolation is accomplished by use of ''default''10X factors. In the case of chlorpyrifos and its oxon, EPA is using a PBPK–PD model as a data-derived approach to estimate PoDs. This model was originally developed by Timchalk and coworkers in 2002 (Refs. 24 and 25), partially funded by EPA Star Grants, and most recently supported by Dow AgroSciences. The PBPK–PD model for chlorpyrifos has been heavily peer reviewed through numerous scientific publications and a review by the FIFRA SAP (Ref. 26). All model code for the PBPK–PD model are provided in the public docket for the chlorpyrifos risk assessment. Developers of the chlorpyrifos PBPK–PD model sponsored a third-party quality assurance assessment to verify model parameter values and their respective sources. EPA has also done a quality assurance assessment of the model for human health risk assessment applications. (Ref. 27).

The chlorpyrifos PBPK–PD model includes the description of a molecular initiating event in the cholinergic toxicity MOA/AOP: AChE inhibition. Thus, the PBPK–PD model can be used to predict the dose metrics associated with cholinergic toxicity following chlorpyrifos exposure, *i.e.,* RBC and brain AChE inhibition. The model also predicts levels of chlorpyrifos, its oxon, and TCPy in various tissues, such as plasma and urine. Age-specific parameters are incorporated allowing for lifestage-specific evaluations from infant through adulthood. The model can be run in two modes: deterministic and variation. In the deterministic mode, the output accounts for human specific metabolism and physiology, thus obviating the need for the inter-species extrapolation factor for all age groups. In variation mode, distributions for 16 parameters, which are critical for determining human variations in RBC AChE inhibition, are incorporated and thus the output accounts for intra-species extrapolation for infants, toddler, youths, and non-pregnant adults. The approach to intra-species extrapolation is described in Unit VI.A.5.

With respect to AChE inhibition, as noted, EPA typically uses a 10% response level in its human health risk assessments. This response level is consistent with EPA's 2006 OP cumulative risk assessment (Ref. 12) and other single chemical OP risk assessments. As such, EPA has used the PBPK–PD model to estimate exposure levels resulting in 10% RBC AChE inhibition following single day (acute; 24 hours) and 21-day exposures for a variety of exposure scenarios. The model accounts for PK and PD characteristics to derive age, duration, and route specific PoDs (see Table 1 below). Separate PoDs have been calculated for dietary (food, drinking water) and residential exposures by varying inputs on types of exposures and populations exposed. Specifically, the following characteristics have been evaluated: Duration (acute, 21-day (steady state)); route (dermal, oral, inhalation); body weights which vary by lifestage; exposure duration (hours per day, days per week); and exposure frequency (events per day (eating, drinking)).

For each exposure scenario, the appropriate body weight for each age group or sex was modeled as identified from the Exposure Factors Handbook (Ref. 28) for residential exposures and from the NHANES/WWEIA Survey (Ref. 29) for dietary exposures.

EPA evaluated the following scenarios: dietary exposure to the oxon exposures via drinking water (24-hour and 21-day exposures for infants, children, youths, and female adults); exposure to chlorpyrifos exposures via food (24-hour and 21-day exposures for infants, children, youths, and female adults); 21-day residential exposures to chlorpyrifos via skin for children, youths, and female adults; 21-day residential exposures to chlorpyrifos via hand-to-mouth ingestion for children 1–2 years old; and 21-day residential exposures to chlorpyrifos via inhalation for children 1–2 years old and female adults.

For all residential dermal exposures to chlorpyrifos, EPA set the fraction of skin in contact with chlorpyrifos to 50% and assumed a daily shower (*i.e.,* washing off the chlorpyrifos) following chlorpyrifos exposure. All residential exposures were set to be continuous for 21 days. For residential exposures via golfing on treated turf, the daily exposure time is assumed to be 4 hours/day; for residential exposures via contact with turf following public health mosquitocide application, the daily exposure duration is assumed to be 1.5 hours. For residential inhalation exposures following public health

mosquitocide application, the exposure duration was set to 1 hour per day for 21 days. The exposure times selected are based on those recommended in the 2012 *Standard Operating Procedures for Residential Pesticide Exposure Assessment* (2012 Residential SOPs). (Ref. 30).

Summarized in Table 1 are the PBPK–PD model results used to estimate exposure levels resulting in 10% RBC AChE inhibition for each evaluated population.

TABLE 1—CHLORPYRIFOS PBPK MODELED DOSES (PODS) CORRESPONDING TO 10% RBC ACHE INHIBITION [1]

| RA Type | Exposure pathway (all chlorpyrifos unless noted) | Infants ( < 1 yr old) | | Young Children (1–2 years old) | | Children (Residential: 6–11 years old; Dietary: 6–12 years old) | | Youths (Residential: 11–16 years old; Dietary: 13–19 years old) | | Females (13–49 years old) | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Acute | Steady state (21 day) | Acute | Steady state (21 day) | Acute | Steady state (21 day) | Acute | Steady state (21 day) | Acute | Steady state (21 day) |
| Dietary | Drinking Water (oxon conc, ppb). | 1,183 | 217 | 3,004 | 548 | 7,700 | 1,358 | 4,988 | 878 | 5,285 | 932 |
| | Food (ug/kg/day) | 600 | 103 | 581 | 99 | 530 | 90 | 475 | 80 | 467 | 78 |
| Residential (Golfers). | Dermal (ug/kg/day) | | | | | | 25,150 | | 16,370 | | 14,250 |
| Residential (Mosquitocide Application). | Dermal (ug/kg/day) | | | | 187,000 | | | | | | 38,650 |
| | Oral (ug/kg/day) | | | | 101 | | | | | | |
| | Inhalation (concn. in air mg/m3). | | | | 2.37 | | | | | | 6.15 |

[1] Empty cells are not populated because these exposure scenarios are either not relevant for the age group (*e.g.,* infants or 1–2 year olds golfing), or do not represent the most health protective life stage for assessment of a particular exposure scenario as recommended in the 2012 SOPs (*e.g.,* for mosquitocide exposure assessment, children 1 to < 2 years old result in a more protective assessment than infants).

*5. Use of the Chlorpyrifos PBPK±PD Model to Extrapolate from Animals to Humans (Inter-species) and Among the Human Population (Intra-species).* Once EPA determines the appropriate toxicological PoDs (Table 1), it then applies appropriate uncertainty factors or DDEFs to account for inter-species and intra-species variation, and to address the requirements of section 408(b)(2)(C) regarding the need for an additional margin of safety for infants and children. Specifically, the modeled doses (PoDs) in this table are divided by appropriate factors to establish PADs that are used for regulatory purposes. The PADs are presented in Unit VI.B.2.ii and iii, Tables 2 and 3.

In a typical risk assessment, the agency uses PoDs derived from laboratory animal studies. For these typical assessments, the agency must then extrapolate from animals to humans which is generally performed with a 10X inter-species factor. As noted above in Unit V.A., the output of the chlorpyrifos PBPK–PD model accounts for human specific metabolism and physiology, thus obviating the need for the inter-species extrapolation factor for all age groups.

EPA has, however, calculated a DDEF to address intra-species variation not accounted for in the output of the PBPK–PD model. Consistent with EPA's ''Guidance for Applying Quantitative Data to Develop Data-Derived Extrapolation Factors for Interspecies and Intraspecies Extrapolation'' (Ref. 31), when calculating a DDEF, EPA compares the administered doses leading to the response level of interest (10% change in RBC AChE inhibition) between a measure of average response and response at the tail of the distribution representing sensitive individuals. Dow AgroSciences has conducted an analysis to derive the oral doses that cause 10% RBC AChE inhibition in both adults and 6-month old infants. (Ref. 1 at 69–70). The ratio of the adult $ED_{10}$ (effective dose) to the infant $ED_{10}$ was then used to derive intraspecies extrapolation factors. In the subsequent Monte Carlo simulations, the target age group is six month old individuals. Based on the 1st percentile of the distributions being used to extrapolate human health, the DDEF for intraspecies extrapolation is 4X for chlorpyrifos and 5X for the oxon (Ref. 32) for all groups except women who are pregnant or may become pregnant.

While the current PBPK–PD model accounts for age-related growth from infancy to adulthood by using polynomial equations to describe tissue volumes and blood flows as a function of age, the model does not include any descriptions on physiological, anatomical and biochemical changes associated with pregnancy. Due to the uncertainty in extrapolating the current model predictions among women who may be pregnant, EPA is applying the standard 10X intra-species extrapolation factor for women of child bearing age.

*6. Retention of the statutory 10X FQPA Safety Factor for purposes of this proposed rule for infants, children, youths, and women of childbearing age for all exposure scenarios.* Section 408 of FFDCA provides that EPA shall apply an additional tenfold margin of safety for infants and children in the case of threshold effects to account for prenatal and postnatal toxicity and the completeness of the data base on toxicity and exposure unless EPA determines that a different margin of safety will be safe for infants and children. Margins of safety are incorporated into EPA assessments either directly through use of a margin of exposure analysis or through using uncertainty (safety) factors in calculating a dose level that poses acceptable risk to humans.

In applying the FQPA safety factor provision, EPA has interpreted the statutory language as imposing a presumption in favor of applying an additional 10X safety factor (Ref. 33). Thus, EPA generally refers to the additional 10X factor as a presumptive or default 10X factor. EPA has also made clear, however, that the presumption can be overcome if reliable data demonstrate that a different factor is safe for infants and children. (Ref. 33). In determining whether a different factor is safe for infants and children, EPA focuses on the three factors listed in section 408(b)(2)(C)—the completeness of the toxicity database, the completeness of the exposure database, and potential pre- and post-natal toxicity.

In examining these factors, EPA strives to make sure that its choice of a safety factor, based on its weight-of-evidence evaluation, does not understate the risk to infants and

children. New lines of research on chlorpyrifos, notably epidemiological studies, have raised some uncertainty about EPA's risk assessment approach for chlorpyrifos with regard to the potential for neurodevelopmental effects that may arise from prenatal exposure to chlorpyrifos. Over the last several years, the agency has taken a stepwise, objective and transparent approach to evaluate, interpret, and characterize the strengths and uncertainties associated with all the lines of scientific information related to the potential for adverse neurodevelopmental effects in infants and children as a result of prenatal exposure to chlorpyrifos. The agency has evaluated multiple lines of evidence with regard to the potential for neurodevelopmental outcomes associated with exposure to chlorpyrifos. These are summarized below; full details of this analysis can be found in the RHHRA. Given the degree of uncertainty EPA has in the human dose-response relationship for neurodevelopmental effects, EPA is retaining the statutory 10X FQPA Safety Factor for purposes of this proposed rule for infants, children (including youths), and women of childbearing age (to address prenatal exposure to the fetus) for all exposure scenarios.

*i. Neurodevelopmental outcomes in laboratory animals.* There is a considerable and still-growing body of literature on the effects of chlorpyrifos on the developing brain of laboratory animals (rats and mice) indicating that gestational and/or postnatal exposure may cause persistent behavioral effects into adulthood. These data provide support for the susceptibility of the developing mammalian brain to chlorpyrifos exposure. Literature searches have been conducted and periodically updated by EPA to review papers addressing long-term outcomes from developmental exposure. This review has focused on studies in which chlorpyrifos was administered during gestation and/or the pre-weaning period and the offspring are examined at some time after weaning, and on studies using relatively low doses (*e.g.,* 1 mg/kg/day) that would not be expected to produce considerable brain AChE inhibition and resultant cholinergic toxicity.

There are substantial differences in the studies, including critical features of experimental design such as developmental period of exposure, dosing scenarios, testing methods, age at testing, and statistical analyses. Despite these differences, behavioral changes of some sort were reported in most studies. Given the wide array of testing that has been conducted, some variability is not unexpected and in fact, the consistency of finding neurological effects is striking. After presentation of these reviews, FIFRA SAP Panels (Refs. 9 and 10) have agreed that exposure to doses of 1 mg/kg/d and greater, during some developmental period, produce significant and long-term effects on animal behavior.

Many of these studies using various cognitive tests report perturbations of learning and/or memory, even though in a few cases these may be manifested as improved function. Several findings using specific test methods have been replicated across studies and laboratories, increasing confidence in the outcomes. Likewise, alterations in some domains, such as those describing anxiety and social interactions, are not fully consistent, but are still suggestive of long-term impacts on these behaviors. Motor activity measures, on the other hand, produce results as varied as the different measures of assessment. Taken together, these data provide evidence for more global alterations in neurobehavioral function rather than a specific profile of effects.

In these papers, testing was conducted at various times after weaning (adolescents to adults), and there is a presumption that the effects are permanent; however, no study has directly addressed this issue. Dose-response is not always evident, since many studies only use one dose, and of those using two or more doses, there is not always a monotonic response. There are differences in route of administration (oral, subcutaneous) and vehicle (corn oil, DMSO), but the outcomes do not provide obvious differences due to these factors. Likewise, the experimental literature has not consistently shown that any specific developmental period is critical overall to the long-term outcomes. For example, using one specific test cognitive changes were observed following gestational and early postnatal, but not late postnatal, exposures (Refs. 34, 35, 36, and 37). On the other hand, deficits have been reported using a different cognitive test following both gestational and late postnatal exposures (Refs. 38, 39, and 40). Similarly, some changes in anxiety and social behaviors were reported at both gestational and postnatal exposure periods. Unfortunately, no laboratory has provided systematic comparisons across exposure period, dosing regimen, and age of testing; such studies would improve understanding of the impact of these critical factors.

These studies have almost exclusively focused on doses that could produce some degree, however minimal, of AChE inhibition. For example, a number of papers use a dose of 1 mg/kg/d administered 1–4 days after birth, and this dose inhibits 5–10% of brain AChE in the pups when measured 2 hours after the last dose (*e.g.,* Refs. 34, 37, and 41). In another study of chlorpyrifos administered in feed to pregnant rats, the lowest intake of 0.36 mg/kg/d produced about 20–25% RBC ChE inhibition in the dams (Ref. 42). Currently there are no animal studies that support or dispute the potential for adverse neurodevelopmental outcomes at lower doses that do not inhibit AChE at any time, since this has not been adequately studied.

Overall, across the literature on neurodevelopmental outcomes and including most recent publications, there continue to be reports of effects on cognitive, anxiety/social behaviors, and motor activity. There are, however, inconsistencies in these effects with regards to dosing paradigms and gender-specificity. Studies report effects at doses that inhibit fetal/pup brain AChE activity to some degree, but there are also studies with no effects at the same doses. The broad profile of neurological effects that has been reported do not aid in the development of a specific AOP (AChE inhibition or other mechanisms), and existing experimental studies have not been designed to examine and track possible mechanisms from early initiating events to the final neurological outcome.

*ii. Modes of action/adverse outcome pathways (MOA/AOP).* Mode of action (MOA) and adverse outcome pathways (AOPs) describe a set of measureable key events that make up the biological processes leading to an adverse outcome and the causal linkages between such events. A review of the scientific literature on potential MOA/AOP leading to effects on the developing brain was conducted for the 2012 FIFRA SAP meeting (Ref. 10) and updated for the December 2014 chlorpyrifos RHHRA (Ref. 1). In short, multiple biologically plausible hypotheses and pathways are being pursued by researchers including: AChE as a morphogen; cholinergic system; endocannabinoid system; reactive oxygen species; serotonergic system; tubulin, microtubule associated proteins, and axonal transport. However, no one pathway has sufficient data to be considered more plausible than the others. Among the available studies, there are effects which are either as or more sensitive than AChE inhibition. The fact that there are, however, sparse data to support the *in vitro* to *in vivo* extrapolation, or the extrapolation from biological perturbation to adverse consequence significantly limits their quantitative

use in risk assessment. The SAP concurred with the agency in 2008 and 2012 about the lack of definable key events in a MOA/AOP leading to developmental neurobehavioral effects. The lack of an established MOA/AOP makes quantitative use of the epidemiology study in risk assessment challenging, particularly with respect to dose-response, critical duration of exposure, and window(s) of susceptibility. The agency will continue to monitor the scientific literature for studies on the MOA/AOP for neurodevelopmental effects.

*iii. Epidemiology studies in mothers and children.* In the chlorpyrifos RHHRA, EPA included epidemiologic research results from three prospective birth cohort studies. These include: (1) The Mothers and Newborn Study of North Manhattan and South Bronx performed by the Columbia Children's Center for Environmental Health (CCCEH) at Columbia University; (2) the Mt. Sinai Inner-City Toxicants, Child Growth and Development Study or the ''Mt. Sinai Child Growth and Development Study'' (Mt. Sinai); and (3) the Center for Health Assessment of Mothers and Children of Salinas Valley (CHAMACOS) conducted by researchers at University of California Berkeley. In these epidemiology studies, mother-infant pairs were recruited for the purpose of studying the potential health effects of environmental exposures during pregnancy on subsequent child development. Importantly, each of these cohorts evaluated the association between prenatal chlorpyrifos or OP exposure with adverse neurodevelopmental outcomes in children through age 7 years.

These studies reflect different types of exposed groups in the total population which strengthens the weight of the evidence considerations regarding this stream of information. The CCCEH Mother's and Newborn study and the Mt. Sinai Child Growth and Development study participants were likely exposed to OPs through the diet and through residential use of the pesticide for indoor pest control. In the residential setting, study populations were most likely exposed through indoor residential use of the pesticide during the study time period and additionally exposed to OPs via the oral route through ingesting residues in the diet and from hand-to-mouth contact with in-home surfaces, as well as possible dermal or inhalation exposure through contact with treated areas in the home environment (Refs. 43, 44, 45, and 46). In contrast, CHAMACOS cohort participants were employed as farm laborers or were residing in homes with farm laborers. The CHAMACOS study participants likely experienced exposure to OPs through the diet and from occupational exposure (primarily inhalation and dermal routes), as well as probable indirect take-home exposures (the ''tracking in'' of pesticide residues through shoes and clothing, augmented by poor hygiene practices) (Ref. 47). In each of the three U.S. children's health cohorts, EPA has considered the strengths and limitations of these studies, and believes that random or systematic errors in the design, conduct or analysis of these studies were unlikely to fully explain observed positive associations between *in utero* OP exposure and adverse neurodevelopmental effects observed at birth and through childhood (age 7 years). EPA believes these are strong studies which support a conclusion that OPs likely played a role in these outcomes.

These cohort studies each enrolled pregnant women during roughly the same time period, measured both environmental exposure to the pesticide during pregnancy and also measured biomarkers representing internal dose during pregnancy and at delivery, and prospectively assessed associations in their newborns and young children through age 7 years. Each study includes several hundred (approximately 100–400) mother-infant pairs; these sample sizes are sufficient to perform statistically valid analyses. Investigators from each study cohort utilized a similarly strong study design (prospective birth cohort); measured pesticide exposure using several different methods including environmental indicators as well as specific and non-specific biomarkers of OPs; ascertained developmental outcomes using validated assessment tools well-established in both clinical and research settings; and, measured, analyzed, selected and statistically adjusted for potentially confounding variables including socio-economic status and other environmental exposures using reasonable and appropriate methods. Limitations exist as well. These studies utilized a one-time measure (or the average of two measures) of chlorpyrifos or OP exposure to assess prenatal pesticide exposure throughout the gestational period, were unable to assess the influence of mixtures (co-occurring exposures in the relevant biological time window), and reflect a small sample size to fully evaluate the effect of more than one simultaneous exposure on neurodevelopment, *i.e.,* evidence of effect modification.

As noted, two major uncertainties in environmental epidemiology studies are the accurate and reliable measurement of exposure and potential confounding variables such as the influence of mixtures. The researchers with each of the three cohorts have provided supplemental methodological research to address these areas to the extent possible. Across the three children's health cohorts, study authors measured biomarkers of OP exposure. There is uncertainty as to the extent measurement of non-specific metabolites of OP or chlorpyrifos accurately reflects OP exposure; CCCEH and Mt. Sinai studies do not estimate post-natal exposure to chlorpyrifos among child participants, therefore the influence of early life and childhood OP exposure is unaccounted for in these analyses. The CHAMACOS cohort measured urinary levels of dialkyl phosphates (DAPs) in young children and did not observe negative significant associations in relation to neurodevelopment from post-natal exposure (Ref. 48). The CHAMACOS cohort investigators also measured AChE and butyl ChE as supplemental indicators of OP exposure.

Potential confounding bias is another major uncertainty within environmental epidemiology studies. Confounding variables, exposures that could be related to OP exposure and neurodevelopmental outcomes such as blood lead, may result in an incorrect epidemiological risk estimate. Across these cohort studies, investigators collected relevant information concerning demographic characteristics and other environmental exposures, and were, to the extent possible with the existing information, able to effectively hold constant the influence of these other variables when estimating the association between prenatal chlorpyrifos and adverse neurodevelopmental outcomes. Control of these variables is important to reduce the chances of a false positive study result. Overall, statistical analyses were judged to be appropriate and reasonable (not overly large number of statistical model variables) to the research question by EPA and expert Panel reviews (Refs. 9 and 10).

Researchers with both the Mt. Sinai and CHAMACOS cohorts evaluated neonatal neurological functioning in association with prenatal OP exposure; CCCEH did not conduct these measurements. To measure indices of abnormal neonatal behavior and/or neurological integrity, the Mt. Sinai and CHAMACOS authors used outcome measures derived from the Brazelton Neonatal Behavioral Assessment Scale

(BNBAS), a neurological assessment of 28 behavioral items and 18 primitive reflexes. This tool was administered to infants 2–5 days post-partum by trained neonatologists in the hospital setting using similar environmental conditions. The authors with both study groups observed an increased number of abnormal reflexes in relation to increasing measures of OP exposure (Refs. 49 and 50). Among the other 27 measures in the BNBAS, neither study group reported evidence of any other positive associations. The authors also observed evidence of potential effect modification by PON1 activity level in the relation between DAPs and neonatal neurodevelopment in which infants of mothers who are slower metabolizers have greater risk of abnormal reflexes (Refs. 49 and 50). However, EPA notes these studies are likely under-powered to make a statistically robust estimate of this statistical interaction.

Researchers across the three children's health cohorts utilized the Bayley Scales of Infant Development II (BSID–II) to generate a Mental Development Index (MDI) and a Psychomotor Development Index (PDI) to assess neurodevelopment in early childhood. In the CCCEH Mothers and Newborn study, Rauh *et al.* (Ref. 51) investigated MDI and PDI at 12, 24, and 36 months of age. Children were categorized as having either high (>6.17 pg/g) or low (≤6.17 pg/g) prenatal chlorpyrifos exposure, using categories informed by results of the previous study on birth characteristics (Ref. 52). Authors reported that the difference in MDI scores was ''marginally significant'' (p = 0.06) between the ''high'' and ''low'' exposed groups; the high exposed group scoring an average of 3.3 points lower than the low exposed (Ref. 51). Regarding the PDI score (motor skills), none of the 12 or 24 month PDI scores showed significant effects, but the 36 month score was significantly related to chlorpyrifos exposure. Researchers noted that the effects were most pronounced at the 36 month testing period. Within the 36 month testing period, the likelihood of highly exposed children developing mental delays were significantly greater (MDI: 2.4 times greater (95% CI: 1.12–5.08, p = 0.02) and PDI: 4.9 times greater (95% CI: 1.78–13.72; p = 0.002)) than those with lower prenatal exposure (Id.). Within the Mt. Sinai study, authors administered the BSID–II to participating children at 12 and 24 months and observed that prenatal total DAP metabolite level was associated with a decrement in mental development at 12 months among blacks and Hispanic children; however, these associations either attenuated or were non-existent at the 24-month visit (Ref. 52). In the CHAMACOS cohort, Eskenazi *et al.* (Ref. 53) observed that prenatal DAP levels were adversely associated with MDI, and at 24 months of age these associations reached statistical significance. In this study, neither prenatal DAPs nor maternal TCPy were associated with PDI (motor skills), nor did authors observe evidence of different risk by PON1 status. (Ref. 54).

With respect to the findings related to the autism spectrum, from CCCEH, Rauh *et al.* (Ref. 51) reported a statistically significant odds ratio for pervasive developmental disorder (PDD) (OR = 5.39; 95% CI: 1.21–24.11) when comparing high to low chlorpyrifos exposure groups. As described above, among 7–9 years old children in the Mt. Sinai Cohort (Ref. 55), there was no overall statistically significant association between maternal third trimester urinary DAP metabolite levels and reciprocal social responsiveness. However, some evidence of modification of the association between prenatal OP pesticide exposure and impaired social responsiveness in early childhood was observed by both race/ethnicity and child sex, with an association between diethyl alkylphosphate (DEAP) and poorer social responsiveness observed among black participants and boys. No association was observed among whites or Hispanics, among girls, or for DAP or dimethyl alkylphosphate (DMAP) biomarker levels. In the CHAMACOS cohort, Eskenazi *et al.* (Ref. 54) reported non-significant, but suggestive, increased odds of PDD of 2.0 (0.8 to 5.1; p = 0.14), whereas Eskenazi *et al.* (Ref. 53) reported a statistically significant association between total DAP exposure and increased odds of PDD.

With respect to attention problems, Rauh *et al.* (Ref. 50) also investigated 36-month child behavior checklist (CBCL) (behavioral) scores. Significant differences were observed between the high and low chlorpyrifos exposure groups in the general category of attention-problems (p = 0.010), and in the more specific DSM–IV (Diagnostic and Statistical Manual of Mental Disorders version IV) scale for ADHD problems (p = 0.018). The CHAMACOS cohort also investigated attention problems in early childhood using three different assessment tools: maternal report of child behavior at 3.5 and 5 years of age; direct assessment of the child at 3.5 and 5 years; and by a psychometrician's report of the behavior of the child during testing at 5 years. In this study population, higher concentrations of OP metabolites in the urine of pregnant women were associated with increased odds of attention problems and poorer attention scores in their children at age 5 years. (Ref. 53).

To measure intelligence among school aged children, authors from each of the three children's health cohorts used the Wechsler Intelligence Scale for Children, 4th edition (WISC–IV). The instrument measures four areas of mental functioning: The Verbal Comprehension Index, the Perceptual Reasoning Index, the Working Memory Index, and the Processing Speed Index. A Full-Scale IQ score combines the four composite indices. WISC–IV scores are standardized against U.S. population-based norms for English and Spanish-speaking children. In the CCCEH Mothers and Newborn Study, Rauh *et al.* (Ref. 56) evaluated the relationship between prenatal chlorpyrifos exposure and neurodevelopment among 265 of the cohort participants who had reached the age of 7 years and had a complete set of data including prenatal maternal interview data, prenatal chlorpyrifos marker levels from maternal and/or cord blood samples at delivery, postnatal covariates, and neurodevelopmental outcome data (Ref. 56). While models were developed using continuous measures of both prenatal chlorpyrifos exposure and Wechsler scores, for ease of interpretation, investigators reported that for each standard deviation increase in exposure (4.61 pg/g) there is a 1.4% reduction in Full-Scale IQ and a 2.8% reduction in Working Memory. In the Mt. Sinai study, prenatal maternal DEP urinary metabolite concentrations were associated with slight decrements in Full Scale Intelligence Quotient (FSIQ), Perceptual Reasoning, and Working Memory between the ages of 6 and 9 years, and difference in intelligence measures by putative PON1 status were also noted. (Ref. 52). Similarly, in the CHAMACOS cohort, Bouchard *et al.* (Ref. 57) observed evidence of an association between prenatal exposures to OPs as measured by urinary DAP (total DAP, DEP, and DMP) metabolites in women during pregnancy, and decreased cognitive functioning in children at age 7. In this study, children in the highest quintile of maternal DAP concentrations had a statistically significant 7 point difference in IQ points compared with those in the lowest quintile.

To ascertain whether observed differences in neurodevelopment after prenatal chlorpyrifos exposure may be explained by differences in brain morphology between exposed groups,

the CCCEH study investigators compared MRI brain images between high and low chlorpyrifos exposed child study participants. (Ref. 58). Authors determined there were distinct morphological differences in brain areas associated with these neurodevelopmental outcomes. The pilot study included 40 child participants due to strict inclusion and exclusion criteria, and the high cost of performing the imaging studies on each child. EPA convened a Federal Panel of experts to perform a written peer-review of this study. (Ref. 59). The Federal Panel concurred with the authors' conclusions in general; however the Federal Panel also noted that significantly greater and more sophisticated MRI imaging studies would be needed to link the morphological changes indicated in this study with specific functional outcomes noted in the CCCEH IQ study. Therefore, while generally supportive of the epidemiologic findings, additional study is needed to make specific links with areas of brain development change.

In sum, across these three children's environmental health studies, authors consistently identified associations with neurodevelopmental outcomes in relation to OP exposure. There is evidence of delays in mental development in infants (24–36 months), attention problems and autism spectrum disorder in early childhood, and intelligence decrements in school age children who were exposed to chlorpyrifos or OPs during gestation. Investigators reported strong measures of statistical association across several of these evaluations (odds ratios 2–4 fold increased in some instances), and observed evidence of exposures-response trends in some instances, *e.g.,* intelligence measures.

7. *Weight-of-Evidence Analysis Across Multiple Lines of Evidence.* The discussion above summarized key scientific information on two different adverse health outcomes: AChE inhibition and potential neurodevelopmental effects. The agency has conducted a weight-of-evidence (WOE) analysis utilizing the draft ''Framework for Incorporating Human Epidemiologic & Incident Data in Health Risk Assessment'' in an effort to integrate this information in the development of an appropriate PoD for chlorpyrifos. That assessment focuses on two key scientific questions: (1) The degree to which scientific data suggest that chlorpyrifos causes long-term neurodevelopmental effects from fetal or early life exposure and (2) the degree to which adverse effects can be attributed to doses lower than those which elicit 10% inhibition of AChE, *i.e.,* the dose levels previously used for regulatory decision making.

i. *Dose-response relationships and temporal concordance.* Since the MOA(s)/AOP(s) is/are not established for neurodevelopmental outcomes, it is not possible to describe the concordance in key events or biological steps leading to neurodevelopmental outcomes. As such, the quantitative linkages between molecular initiating events, intermediate steps, and ultimately the adverse outcome (*i.e.,* neurodevelopmental effects) cannot be determined. Experimental toxicology studies in rodents suggest that long-term effects from chlorpyrifos exposure may occur. Due to the dose selections in most of these *in vivo* studies evaluating effects such as behavior and cognition, it is not known whether such adverse effects would be shown at doses lower than those which elicit 10% RBC AChE inhibition. It is notable, however, that comparing the lowest NOAEL observed in the *in vivo* animal studies (0.2 mg/kg/day; Ref. 60) for the neurodevelopmental outcomes to the repeated dosing reliable $BMDL_{10}$ ranging from 0.05–0.17 mg/kg/day for RBC AChE inhibition suggests that neurodevelopmental outcomes may occur in the same range as AChE inhibition in rat.

Within the epidemiology studies, the relationship in time between prenatal chlorpyrifos exposure and adverse neurodevelopmental outcomes is concordant. Specifically, with regard to the children's environmental health epidemiology studies, each of the three study cohorts utilized a prospective birth cohort study design in which mothers were recruited into study prior to the birth of the infants and development and identification of adverse effects; therefore, it is known with certainty that exposure preceded effect. In addition, because the time period under study within these cohorts, and specifically the CCCEH study, spanned the point in time in which pesticide manufacturers voluntarily cancelled the use of chlorpyrifos in the home environment, researchers were able to show the change in exposure before (high use period) and after (low/no use period) the period of removal of chlorpyrifos products from the residential marketplace. Moreover, prior to the voluntary cancellation there were >80% detectable levels of chlorpyrifos in cord blood but in the time period after the cancellation only 16% of the measured values were greater than the LOD; there was only one child born in the time period subsequent to the voluntary cancellation of chlorpyrifos in the residential marketplace for whom the cord blood chlorpyrifos level was in the upper-tertile of pre-cancellation exposure levels. The significantly reduced proportion of measured values greater than the limit of detection as well as the observation of an absence of an association between prenatal chlorpyrifos exposure and neurodevelopmental outcomes among infants born after the voluntary cancellation of chlorpyrifos support the hypothesis that chlorpyrifos is related to these outcomes. However, as noted by study authors, EPA, and the FIFRA SAP (Ref. 10), this could also be due to an inadequate sample size to detect a small to modest effect among the group of infants born after the voluntary cancellation.

With respect to the timing of exposure, the cord blood and other (meconium) measures from the CCCEH study provide evidence that exposure did occur to the fetus during gestation but the actual level of such exposure during the critical window(s) of susceptibility is not known. While significant uncertainties remain about the actual exposure levels experienced by mothers and infant participants in the three children's health cohorts, particularly during the time period prior to the voluntary cancellation of indoor residential uses of chlorpyrifos, exposures measured in the range reported in the epidemiology studies (pg/g plasma) are likely low enough that they were unlikely to have resulted in AChE inhibition. The FIFRA SAP (Ref. 10) concurred with the conclusion that measured levels of chlorpyrifos among epidemiology study participants were unlikely to have resulted in AChE inhibition. The urinary TCPy concentrations among mothers were comparable to the general population levels measured in NHANES. Comparing cord blood concentrations with the concentrations in which AChE inhibition was observed in adult volunteers indicates AChE inhibition would likely not have occurred at levels observed in the epidemiology studies (6.17 pg/g). Therefore, while uncertainty exists as to actual chlorpyrifos exposure at (unknown) critical windows of exposure, EPA believes it is unlikely mothers enrolled in the birth cohort studies experienced RBC AChE inhibition (greater than 10%).

The biomarker data from the CCCEH studies are supported by EPA's dose reconstruction analysis using the PBPK–PD model, which support a conclusion that indoor application of chlorpyrifos, when used as allowed prior to cancellation from the residential

marketplace in 2000, likely would not have resulted in RBC AChE inhibition greater than 10% in pregnant women or young children.

*ii. Strength, consistency, and specificity.* As stated in the EPA neurotoxicity guidelines (Ref. 61), direct extrapolation of developmental neurotoxicity results from laboratory animals to humans is limited by the lack of knowledge about underlying toxicological mechanisms and the relevance of these results to humans. EPA notes consistencies across these two databases, although challenges of making a direct comparison between neurodevelopmental domain inter-species remain. It can be assumed that developmental neurotoxicity effects in animal studies indicate the potential for altered neurobehavioral development in humans, although the specific types of developmental effects seen in experimental animal studies may not be the same as those that may be produced in humans. However, considering the toxicological and epidemiological data in the context of three major neurodevelopmental domains (specifically, cognition, motor control, and social behavior), insights can be gained. For example, chlorpyrifos studies in rats and/or mice have reported impaired cognition (spatial learning and working memory; *e.g.,* Refs. 35 and 38); changes in locomotor activity levels (exploration, rearing; *e.g.,* Refs. 36 and 62); altered social interaction (aggression, maternal behavior; Refs. 63 and 64); and effects on brain morphometrics (Refs. 65 and 66). Similarly, epidemiologic investigations have reported effects on cognition (Bayley scale indices; Refs. 50 and 53), abnormal motor development in neonates (reflexes, Brazelton score; Refs. 49 and 48), altered social development (*e.g.,* ADHD; Refs. 50 and 67), and MRI brain scans (Ref. 68). 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 (age, protocol). Likewise, observational epidemiology studies vary by population characteristics (race/ethnicity, socio-economic status (SES), and pesticide use/exposure profile), co-exposures (mix of chemicals, windows of exposure), and method of exposure and outcome assessment. Given the differences across laboratory animal and epidemiology studies, the qualitative similarity in research findings is striking.

In contrast, quantitatively, there are notable differences between animals and humans. Specifically, in animals, the doses most often used in the behavior studies (1 and 5 mg/kg/day) are sufficient to elicit approximately ≥10% brain AChE inhibition and ≥30% in RBC AChE inhibition, depending on the study design, age of the animal, and sampling time. In the epidemiology studies, based on the comparisons with biomonitoring data and the results of the dose-reconstruction analysis, it is unlikely that RBC AChE would have been inhibited by any meaningful or measurable amount, if any at all, and most likely none in the brain. This key difference in dose response between the experimental toxicology and epidemiology studies poses challenges in interpreting such data. There are a number of possible hypotheses such as: (1) Limitations of experimental laboratory studies which have limited statistical power due to relatively small sample sizes; (2) humans display a broader array of behaviors and cognitive abilities than rats, thus limiting the sensitivity of the rat studies; and (3) in the epidemiology studies, the timing of chlorpyrifos application and blood collections are not coupled—thus higher levels of blood chlorpyrifos were likely missed (albeit the results of the dose reconstruction analysis reduce the likelihood of this hypothesis).

In making a weight-of-the-evidence analysis, it is important to consider the strength of the statistical measures of association between prenatal chlorpyrifos exposure and adverse neurodevelopmental outcomes through childhood (epidemiology) and possibly into adulthood (animal studies). It is also important to consider the strength of the integrated qualitative and quantitative evidence, the consistency of the observed associations across epidemiology studies and considering both animal and human data support the conclusion that chlorpyrifos plays a role in adverse neurodevelopmental outcomes. While it cannot be stated that chlorpyrifos alone is the sole contributor to the observed outcomes (specificity), since other environmental, demographic or psychosocial exposures may also play a part in these outcomes, this does not obviate the contribution of prenatal chlorpyrifos exposure in the development of adverse neurodevelopmental outcomes as echoed by the FIFRA SAP (Ref. 10).

The CCCEH study, which measures chlorpyrifos specifically, provides a number of notable associations. Regarding infant and toddler neurodevelopment, the CCCEH authors also reported statistically significant deficits of 6.5 points on the Bayley Psychomotor Development Index (PDI) at 3 years of age when comparing high to low exposure groups (Ref. 50). Notably these decrements in PDI persist even after adjustment for group and individual level socioeconomic variables (Ref. 69). These investigators also observed increased odds of mental delay (OR = 2.4; 95% CI: 1.1–5.1) and psychomotor delay (OR = 4.9; 95% CI: 1.8–13.7) at age three when comparing high to low exposure groups. (Ref. 50). Rauh *et al.* (Ref. 50) also reported large odds ratios for attention disorders (OR = 11.26; 95% CI: 1.79–70.99), ADHD (OR = 6.50; 95% CI: 1.09–38.69), and PDD (OR = 5.39; 95% CI: 1.21–24.11) when comparing high to low chlorpyrifos exposure groups. (Ref. 50). EPA notes that the magnitude of these results are so large that they are unlikely to be affected by residual confounding although limited sample sizes resulted in imprecise estimates.

Decrements in intelligence measures were identified in relation to increasing levels of prenatal chlorpyrifos exposure. The CCCEH study reported statistically significant decreases of 1.4% in full scale IQ and 2.8% in working memory among seven-year olds for each standard deviation increase in chlorpyrifos exposure. (Ref. 56). These results persist even when performing sensitivity analyses including only those with detectable chlorpyrifos levels.

*iii. Biological plausibility and coherence.* Although MOA(s)/AOP(s) has/have not been established for neurodevelopmental outcomes, the growing body of literature does demonstrate that chlorpyrifos and/or its oxon are biologically active on a number of processes that affect the developing brain. Moreover, there is a large body of *in vivo* laboratory studies which show long-term behavioral effects from early life exposure. EPA considers the results of the toxicological studies relevant to the human population, as qualitatively supported by the results of epidemiology studies. The lack of established MOA/AOP does not undermine or reduce the confidence in the findings of the epidemiology studies. The CCCEH study data are not considered in isolation, but rather are strengthened when considered in concert with the results from the other two cohort studies, as noted by the FIFRA SAP. (Ref. 10). As noted above, the CHAMACOS and Mt. Sinai cohorts that measured neurological effects at birth (the Brazelton index), observed a putative association with chlorpyrifos. (Ref. 48 and 49). Similarly, while not consistent by age at time of testing (ranging from 6 months to 36 months across the three cohorts), each cohort reported evidence of impaired mental and psychomotor development. Attentional problems and ADHD were

reported by both Columbia and CHAMACOS investigators. Finally, each of the three cohort study authors observed an inverse relation between the respective prenatal measures of OP and intelligence measures at age 7 years.

*iv. Weight of evidence conclusions.* Key issues being considered by the Agency in its weight-of-evidence evaluation of chlorpyrifos toxicity are (1) whether chlorpyrifos causes long-term effects from fetal or early life exposure and (2) whether adverse effects can be attributed to doses lower than those which elicit 10% inhibition of AChE—EPA's current regulatory point of departure for chlorpyrifos and other OPs. When taken together the evidence from (1) the experimental toxicology studies evaluating outcomes such as behavior and cognitive function; (2) mechanistic data on possible adverse outcome pathways/modes of action; and (3) epidemiologic and biomonitoring studies leads the agency to the following conclusions:

- Qualitatively, these lines of evidence together support a conclusion that exposure to chlorpyrifos results in adverse neurodevelopmental outcomes in humans, at least under some conditions.
- Quantitatively, the dose-response relationship of AChE inhibition across different life stages is established, but MOAs/AOPs for neurodevelopmental outcomes are not established.
- The database of *in vivo* animal toxicology neurodevelopmental studies on adverse outcomes includes only a small number of studies at doses lower than 1 mg/kg/day. Despite this, the agency noted that the BMD values in adult (pregnant and nonpregnant) female rats (0.05–0.15 mg/kg/day) are generally 10-fold or more lower than the doses where effects on neurodevelopmental outcomes in laboratory rats are observed.
- With respect to the mechanistic data, there are sparse data to support the *in vitro* to *in vivo* extrapolation, or the extrapolation from biological perturbation to adverse consequence, which significantly limits their quantitative use in risk assessment.
- As noted above, the lack of an established MOA/AOP makes quantitative use of the epidemiology study in risk assessment challenging, particularly with respect to dose-response, critical duration of exposure, and window(s) of susceptibility. Despite this uncertainty, the cord blood and other measures (meconium) provide evidence of exposure to the fetus during gestation. Moreover, exposure levels in the range measured in the epidemiology studies (pg/g) are likely low enough that they are unlikely to result in AChE inhibition, as supported by the dose reconstruction analysis of residential use prior to 2000 (although the agency has not investigated the degree to which exposure to multiple AChE-inhibiting pesticides indoors simultaneously could impact this conclusion).
- Given the totality of the evidence, the agency concludes that chlorpyrifos likely played a role in the neurodevelopmental outcomes reported in the CCEH study but uncertainties such as the lack of an established MOA/AOP for neurodevelopmental effects and the exposure to multiple AChE-inhibiting pesticides precludes definitive causal inference.
- In light of the uncertainties regarding the relationship of observed neurodevelopmental outcomes to AChE inhibition, EPA is retaining the 10X FQPA safety factor.

Following publication of the December 2014 RHHRA, EPA received public comments suggesting that the uncertainty surrounding the dose-response relationship for neurodevelopmental effects warranted the application of a larger safety factor than the statutory default 10X factor. The commenters suggested that EPA's assessment had failed to establish that, even with the retained 10X FQPA safety factor, exposures to chlorpyrifos will not result in adverse neurodevelopmental outcomes. Some of the commenters suggested that EPA evaluate available biomonitoring from the epidemiologic data to help assess whether these outcomes could in fact be occurring at levels below EPA's PAD that it is using for purposes of this proposed rule. EPA is currently in the process of evaluating the available biomonitoring; however, in light of the August 10, 2015 *PANNA* decision that orders EPA to respond to the PANNA–NRDC Petition not later than October 31, 2015, EPA has not been able to complete that evaluation in advance of this proposal. EPA is continuing its evaluation of the available biomonitoring and will update this action to reflect the results of that review, if warranted.

Further, EPA is aware that some commenters on EPA's RHHRA believe the PBPK–PD model used to derive PoDs is inappropriate for the evaluation of neurodevelopmental effects, given that there is no established association between AChE inhibition and long term adverse neurodevelopmental outcomes observed in recent epidemiology studies. While EPA's evaluation of biomonitoring from available human epidemiology studies will not help to further determine the MOA/AOP for these adverse neurodevelopmental outcomes, as noted, it will help EPA better assess whether the doses (PADs) EPA is proposing to use for regulatory purposes in this proposed rule are protective for potential adverse neurodevelopmental effects. While, as noted, that assessment is still not complete, because EPA is proposing to revoke all tolerances in this proposed rule based on its concern regarding AChE inhibition, it is unnecessary for EPA to determine at this time whether its current PADs bound the chlorpyrifos exposures measured in the epidemiology studies. In any case, as EPA completes its further evaluation it will update this action, as warranted.

*B. Dietary Exposure and Risk Assessment.*

The general approach for the chlorpyrifos dietary exposure and risk assessment is as follows: The PBPK–PD model was used to predict acute (24 hour) and steady state (21-day) PoDs which correspond to 10% RBC AChE inhibition for the lifestages relevant to chlorpyrifos risk assessment. The PoDs are then divided by the total uncertainty factor to determine the PAD.

For the dietary risk assessment for food only, the exposure values resulting from Dietary Exposure Evaluation Model (DEEM) and the Calendex model are compared to the PBPK–PD-based acute PAD and steady state PAD, respectively. When estimated dietary risk estimates exceeds 100% of the PAD there is generally a risk concern.

For the dietary assessment for water, a drinking water level of comparison (DWLOC) approach to aggregate risk was used to calculate the amount of exposure available in the total 'risk cup' for chlorpyrifos oxon in drinking water after accounting for any chloropyrifos exposures from food and/or residential use.

*1. Residues of concern.* The qualitative nature of the residue in plants and livestock is adequately understood based on acceptable metabolism studies with cereal grain (corn), root and tuber vegetable (sugar beets), and poultry and ruminants. The residue of concern, for tolerance expression and risk assessment, in plants (food and feed) and livestock commodities is the parent compound chlorpyrifos.

Based on evidence (various crop field trials and metabolism studies) indicating that the metabolite chlorpyrifos oxon would be not be present in edible portions of the crops (particularly at periods longer than the currently registered PHIs), it is not a residue of concern in food or feed at this

time. Also, the chlorpyrifos oxon is not found on samples in the USDA PDP monitoring program. In fact, from 2007 to 2012, out of several thousand samples of various commodities, only one sample of potato showed presence of the oxon at trace levels, 0.003 ppm where the LOD was 0.002 ppm, even though there are no registered uses of chlorpyrifos on potato in the U.S.

The oxon metabolite was not found in milk or livestock tissues in cattle and dairy cow feeding studies, at all feeding levels tested, and is not a residue of concern in livestock commodities.

Oxidation of chlorpyrifos to chlorpyrifos oxon can occur through photolysis, aerobic metabolism, and chlorination as well as other oxidative processes. Because of the toxicity of the oxon and data indicating that chlorpyrifos rapidly converts to the oxon during typical drinking water treatment (chlorination), the drinking water risk assessment considers the oxon as the residue of concern in treated drinking water and assumes 100% conversion of chlorpyrifos to chlorpyrifos oxon. (Ref. 70). This approach of assuming 100% conversion of chlorpyrifos to the more toxic chlorpyrifos oxon, is a conservative approach and thus protective of other likely exposure scenarios of chlorpyrifos only and chlorpyrifos and chlorpyrifos oxon.

The chlorpyrifos degradate TCPy is not considered a residue of concern for this assessment as it does not inhibit cholinesterase (a separate human health risk assessment has been performed for TCPy, which has its own toxicity database). TCPy (derived from triclopyr, chlorpyrifos, and chlorpyrifos-methyl) was previously assessed on June 6, 2002. (Ref. 71).

*2. Dietary (food only) risk assessment.* The general approach for the chlorpyrifos (food only) exposure and risk assessment can be described as follows: The PBPK–PD model was used to predict acute (24 hour) and steady state (21-day) PoDs which correspond to 10% RBC AChE inhibition for the index lifestages relevant to chlorpyrifos risk assessment (children of various ages which differ due to exposure pattern, and adult females of childbearing age). The PoDs are then divided by the total uncertainty factor to determine the PAD. For food, the residue of concern is chlorpyrifos (the oxon metabolite is not an expected residue on foods). The chlorpyrifos total uncertainty factors are 100X for adult females (10X FQPA SF and 10X intra-species extrapolation factor) and 40X for the other populations (10X FQPA SF and 4X intra-species extrapolation factor). For the dietary risk assessment for food only, the exposure values resulting from Dietary Exposure Evaluation Model (DEEM) and the Calendex model are compared to the PBPK–PD-based acute PAD and steady state PAD, respectively. The chlorpyrifos exposure values resulting from dietary modeling are compared to the PAD. Dietary exposures greater than 100% of the PAD are generally cause for concern and would be considered ''unsafe'' within the meaning of FFDCA section 408(b)(2)(B).

*i. Description of residue data used in dietary (food only) assessment.* Acute and steady state dietary (food only) exposure analyses for chlorpyrifos were conducted using the Dietary Exposure Evaluation Model (DEEM) and Calendex software with the Food Commodity Intake Database (FCID) (Ref. 90). This software uses 2003–2008 food consumption data from NHANES/WWEIA. The most recent previous dietary assessment was conducted in support of the 2011 PHHRA and the ongoing chlorpyrifos registration review. (Ref. 72). This current analysis reflect the latest consumption data as well as more recent food monitoring and percent crop treated data. These analyses were performed for the purpose of obtaining food exposure values for comparison to the chlorpyrifos doses predicted by the PBPK–PD model to cause RBC ChEI. The acute and steady state exposure analyses do not include drinking water which is assessed separately as discussed in Unit VI.2.B.

Both the acute and steady state dietary exposure analyses are highly refined. The large majority of food residues used were based upon U.S. Department of Agriculture's PDP monitoring data except in a few instances where no appropriate PDP data were available. In those cases, field trial data were used or tolerance level residues were assumed. The same data were used for both the acute and steady state analyses. EPA also considered percent crop treated information. Food processing factors from submitted studies were used as appropriate.

The acute and steady state dietary exposure assessment used percent crop treated information from EPA's Screening Level Usage Analysis (Ref. 73) to estimate chlorpyrifos exposures from the consumption of food. Reported percent crop treated ranged from <2.5% to 70%. 100% crop treated was assumed for many crops for which no usage data were available.

*ii. Acute dietary (food only) risk assessment.* Chlorpyrifos acute (food only) dietary exposure assessments were conducted using the Dietary Exposure Evaluation Model software with the Food Commodity Intake Database DEEM–FCID™, Version 3.16, which incorporates consumption data from NHANES/WWEIA. This dietary survey was conducted from 2003 to 2008. Acute dietary risk estimates are presented below for the sentinel population subgroups for acute risk assessment: infants (<1 year old), children (1–2 years old), youths (6–12 years old) and adults (females 13–49 years old). The assessment of these index lifestages will be protective for the other population subgroups.

As Table 2 indicates, EPA believes that acute dietary risk from food only does not present a significant risk, as estimates are all far below 100% of the acute PAD for food (aPADfood) at the 99.9th percentile of exposure. The subgroup with the highest risk estimate was females (13–49 years old) at 3.2% aPADfood.

TABLE 2—ACUTE DIETARY (FOOD ONLY) EXPOSURE AND RISK ESTIMATES FOR CHLORPYRIFOS

| Population subgroup | $aPoD_{food}$ [1] (ug/kg/day) | $aPAD_{food}$ [2] (ug/kg/day) | Food exposure [3] (ug/kg/day) | Percent of $aPAD_{food}$ |
|---|---|---|---|---|
| Infants (<1 yr) | 600 | 15 | 0.273 | 1.8 |
| Children (1–2 yrs) | 581 | 14 | 0.423 | 3.0 |
| Youths (6–12 yrs) | 530 | 13 | 0.189 | 1.4 |
| Adults (Females 13–49 yrs) | 469 | 4.7 | 0.150 | 3.2 |

[1] Acute point of departure; daily dose predicted by PBPK–PD model to cause RBC ChEI of 10% for acute dietary (food) exposures.

[2] aPAD = acute PAD = PoD (Dose predicted by PBPK–PD model to cause 10% RBC ChEI) ÷ total UF; Total uncertainty factor = 100X for females 13–49 years (10X intraspecies factor and 10X FQPA safety factor) and 40X for other populations (4X intraspecies factor and 10X FQPA safety factor).

[3] Acute food only exposure estimates from DEEM (at 99.9th percentile). Refined with monitoring data and %CT.

*iii. Steady state detary (food only) risk assessment.* A chlorpyrifos steady state dietary (food only) exposure analysis was conducted using Calendex-FCID™. EPA's steady state assessment considers the potential risk from a 21-day exposure duration using a 3-week rolling average (sliding by day) across the year. For this assessment, the same food residue values used in the acute assessment were used for the 21-day duration. In the Calendex software, one diary for each individual in the WWEIA is selected to be paired with a randomly selected set of residue values for each food consumed. The steady state analysis calculated exposures for the sentinel populations for infant, child, youths, and adult (infants <1 year, children 1–2 years, youths 6–12 years, females 13–49 years).

Calendex reported dietary exposures for each population subgroup at several percentiles of exposure ranging from 10th percentile to 99.9th percentile. Similar to acute risks, the dietary (food only) exposures for chlorpyrifos were all well below 100% ssPADfood (all populations, at all percentiles of exposure). Only the 99.9th percentile of exposure is presented in Table 3. For the steady state dietary (food only) exposure analyses, children (1–2 years old) was the population subgroup with the highest risk estimate at 9.7% of the ssPADfood at the 99.9th percentile of exposure.

TABLE 3—STEADY STATE DIETARY (FOOD ONLY) EXPOSURE AND RISK ESTIMATES FOR CHLORPYRIFOS

| Population subgroup | $_{SS}$ $PoD_{food}$ [1] (ug/kg/day) | $ssPAD_{food}$ [2] (ug/kg/day) | Food exposure [3] (ug/kg/day) | Percent of $ssPAD_{food}$ |
|---|---|---|---|---|
| Infants (<1 yr) | 103 | 2.6 | 0.186 | 7.2 |
| Children (1–2 yrs) | 99 | 2.5 | 0.242 | 9.7 |
| Youths (6–12 yrs) | 90 | 2.2 | 0.128 | 5.8 |
| Adults (Females 13–49 yrs) | 78 | 0.78 | 0.075 | 9.6 |

[1] Steady state point of departure; daily dose predicted by PBPK–PD model to cause RBC ChEI of 10% for steady state (21-day) dietary (food) exposures.

[2] ssPAD = Steady state PAD = PoD (Dose predicted by PBPK–PD model to cause 10% RBC ChEI) ÷ total UF; Total uncertainty factor = 100X for females 13–49 years (10X intraspecies factor and 10X FQPA safety factor) and 40X for other populations (4X intraspecies factor and 10X FQPA safety factor).

[3] Steady state (21-day) food only exposure estimates from Calendex (at 99.9th percentile). Refined with monitoring data and %CT.

As Tables 2 and 3 make clear, EPA does not believe that food exposures to chlorpyrifos by themselves present a significant risk of AChE inhibition. Based on the analysis above, EPA would therefore not be proposing the revocation of chlorpyrifos if dietary exposures were confined to food. As outlined below, however, EPA believes that for some portions of the country, food exposures, when aggregated with residential exposures and potentially more significant drinking water exposures, do present a significant risk concern and support revocation of all chlorpyrifos tolerances.

*iv. Residential (non-occupational) exposure/risk characterization.* As explained above in Unit V.B.3., in assessing dietary risk under the FFDCA, EPA must consider not only direct dietary exposure from food and drinking water, but also non-occupational exposures to the pesticide, such as residential exposure and bystander exposure from the use of agricultural pesticides. For simplicity, EPA refers to its assessment of all such exposures as its ''residential exposure assessment.'' For chlorpyrifos, the vast majority of residential use products were cancelled as of 2001. Current chlorpyrifos residential uses now include a granular fire ant mound use (commercial applicator only) and ant and roach bait in child-resistant packaging (homeowner applicator). Additionally, chlorpyrifos is labeled for public health aerial and ground-based fogger ULV mosquito adulticide applications and for golf course turf applications. For the purpose of residential exposure assessment, the parent compound chlorpyrifos is the residue of concern.

With respect to bystander exposure, EPA's worker protection standard prohibits using any pesticide in a way that will contact either workers or bystanders through spray drift. Further, in connection with EPA's 2012 spray drift evaluation, EPA imposed additional no-spray buffers to limit deposition of chlorpyrifos through drift in areas adjacent to agricultural fields where bystanders may be present following application. With respect to bystander exposure to volatilized (vapor form) chlorpyrifos following application, as noted in Unit VI.A., recently submitted rat acute toxicity studies of vapor phase chlorpyrifos along with available subchronic vapor phase inhalation studies support a conclusion that acute exposure to the saturated vapor of chlorpyrifos or its oxon do not result in hazard due to AChE inhibition. Accordingly, EPA concludes that with the additional no spray buffer restrictions, risk concerns to bystanders from spray drift have been eliminated and therefore bystander exposures are not included as part of EPA's aggregate risk assessment.

*Residential Handler Exposure.* EPA uses the term ''handlers'' to describe those individuals who are involved in the pesticide application process. EPA believes that there are distinct tasks related to applications and that exposures can vary depending on the specifics of each task. Residential (non-occupational) handlers are addressed somewhat differently by EPA as homeowners are assumed to complete all elements of an application without use of any protective equipment.

Based upon review of all chlorpyrifos registered uses, only the ant and roach bait products can be applied by a homeowner in a residential setting. Because the ant and roach bait products are designed such that the active ingredient is contained within a bait station, the potential for contact with the chlorpyrifos-containing bait material has been eliminated and therefore these products do not pose a risk concern.

*Residential Post-Application Exposure.* There is the potential for post-application exposures as a result of being in an environment that has been previously treated with chlorpyrifos. Chlorpyrifos can be used in areas frequented by the general population including golf courses and as an aerial and ground-based ULV mosquito adulticide applications made directly in

residential areas. Post-application exposure from residential fire ant mound treatment is not quantitatively assessed here as exposures are considered to be negligible and do not pose a risk concern; these products can only be applied professionally and EPA therefore does not anticipate direct non-occupational exposure with treated ant mounds.

In the RHHRA which supports this rule, EPA has updated the post-application exposure assessment to reflect: (1) Use of the PBPK–PD model for determining toxicological PoDs; (2) use of the 2012 Residential SOPs (Ref. 28); (3) use of the AgDISP model for estimation of airborne concentrations and residue dissipation following chlorpyrifos mosquito adulticide applications; (4) updated methodology for determining the airborne concentration of active ingredient following ground-based mosquito adulticide applications; and (5) use of updated body weights for all residential populations assessed.

In addition, EPA utilized only steady state durations of exposure in the updated residential assessment. The steady state endpoint selection for chlorpyrifos overlaps EPA's traditional short-term exposure duration endpoint selection and is considered health protective for both short- and intermediate-term exposures.

The quantitative exposure/risk assessment for residential post-application exposures is based on the following scenarios:

Golf Course Use (Emusifiable Concentrate (EC) and Granular (G) Formulations)

- Children 6 to <11 years old, youths 11 to <16 years old, and adult post-application dermal exposure from contact with treated turf while golfing.

Public Health Mosquito Adulticide Use (Aerial and Ground Applications)

- Children 1 to <2 years old and adult post-application dermal exposure from contact with turf following the deposition of chlorpyrifos residues from public health mosquito adulticide application.
- Children 1 to <2 years old and adult post-application inhalation exposure from airborne chlorpyrifos following public health mosquito adulticide application.
- Children 1 to <2 years old post-application incidental oral (hand-to-mouth) exposure from contact with turf following the deposition of chlorpyrifos residues from public health mosquito adulticide application.
- Children 1 to <2 years old post-application incidental oral (object-to-mouth) exposure from contact with toys containing residues from turf following the deposition of chlorpyrifos residues from public health mosquito adulticide application.

The following assumptions and exposure factors served as the basis for completing the residential post-application risk assessment. These assumptions and factors are described in detail in the updated occupational and residential exposure and risk assessment. (Ref. 74).

*Exposure Duration:* Residential post-application exposures to chlorpyrifos are assumed to be steady state (*i.e.,* 21 days or longer).

The application of mosquitocide in residential areas may result in the potential for post-application inhalation exposures. The aerosolized particulate remaining following application is assumed to persist for no longer than one hour in proximity of the application source and, accordingly, would be most appropriately defined as acute in duration. However, this assessment assumes that post-application inhalation exposures are steady state which is a highly conservative approach given how infrequently mosquitocides are repeatedly applied to the same locations and how rapidly aerosols dissipate after these types of applications. The parameters used to define this exposure scenario in the PBPK–PD model conservatively reflect daily, one hour exposures for 21 days.

*Application Rates:* In order to seek clarification of chlorpyrifos usage, the agency compiled a master use summary document reflective of the use profile of all active product labels. The document, among other information, presents all registered uses of chlorpyrifos and corresponding maximum single application rates, equipment types, restricted entry intervals (REIs), etc. This assessment assumes that the detailed information on application rates and use patterns presented in Appendix 9 (Master Use Summary Document) in support of the 2014 RHHRA will be implemented on all chlorpyrifos labels and is the basis of the occupational and residential risk assessment. If, for any reason, the final chlorpyrifos labels contain higher application rates, the actual risks posed by those products may exceed the risks estimated in this assessment.

*Body Weights:* The body weights assumed for this assessment differ from those used in 2011 residential exposure assessment and are based on the recommendations of the 2012 Residential SOPs. These body weights are the same as selected for derivation of PBPK–PD PoDs for use in assessment of residential exposures.

The standard body weights are as follows: Youths 11 to <16 years old, 57 kg; children 6 to <11 years old, 32 kg; and children 1 to <2 years old, 11 kg. For adults when an endpoint is not sex-specific (*i.e.,* the endpoints are not based on developmental or fetal effects) a body weight of 80 kg is typically used in risk assessment. However, in this case, a female-specific body weight of 69 kg was used. While the endpoint of concern, RBC AChE inhibition, is not sex-specific, the female body weight was used due to concerns for neurodevelopmental effects related to early life exposure to chlorpyrifos.

Post-application exposures from golfing have been assessed using the 2012 Residential SOPs and with use of exposure data from a chemical-specific turf transferable residue (TTR) study. The study was conducted with an emulsifiable concentrate, a granular, and a wettable powder formulation. Only the emulsifiable concentrate and granular data were used because there are no currently registered wettable powder formulations. The study was conducted in 3 states, California, Indiana and Mississippi, with use of the emulsifiable concentrate and wettable powder formulations. Exposure was estimated by normalizing Day 0 TTR measures from study application rates to the current maximum application rate allowable by the label. Chlorpyrifos oxon residues were not analyzed.

The post-application exposure potential from public health mosquito adulticide applications has been considered for both ground based truck foggers and aerial applications. For assessment of the mosquito adulticide use, the algorithms and inputs presented in the 2012 Residential SOP Lawns/Turf section were used coupled with the available TTR data described above. The deposition of chlorpyrifos from these applications are not based on the application rate alone, but also using the AgDISP (v8.2.6) model (aerial applications, the currently recommended model for assessment of mosquito adulticide applications) or empirical data (ground applications) to determine how much pesticide is deposited on residential lawns as a result of mosquito adulticide treatments at the maximum application rates for each. The TTR data are then used to determine the fraction of the total residue deposited following the mosquitocide application which can result in exposures to impacted individuals. Inhalation exposures are also estimated using AgDrift for aerial

application and a recently developed well-mixed box (WMB) model approach for outdoor foggers.

EPA used the AgDISP (v8.2.6) model to estimate the deposition of chlorpyrifos from aerial applications and the airborne concentration of chlorpyrifos following public health mosquitocide application. AgDISP predicts the motion of spray material released from aircraft, and determines the amount of application volume that remained aloft and the amount of the resulting droplets deposited on the surfaces in the treatment area, as well as downwind from the treatment area. The model also allows for the estimation of air concentrations in the breathing zones of adults and children for use in calculating the post-application inhalation risks to individuals residing in areas being treated by aerial application of chlorpyrifos. The aerial fraction of the mosquito adulticide application rate applied (0.010 lb ai/A) is 0.35 (*i.e.,* 35 percent of application rate is deposited on turf); and the airborne concentration at the breathing height of adults and children of chlorpyrifos 1 hour following aerial mosquito adulticide application is 0.00060 mg/m3.

EPA used empirical data to derive the ground-based deposition of chlorpyrifos following public health mosquitocide application. These data, conducted by Moore *et al.* (Ref. 75) and Tietze *et al.* (Ref. 76), measured the deposition of malathion via ULV ground equipment as applied for mosquito control. Based on these data, EPA used an off-target deposition rate of 5 percent of the application rate to evaluate ground-based ULV applications (*i.e.,* 5 percent of the target application rate deposits on turf). A value slightly higher than the mean values for both studies was selected because of the variability in the data and the limited number of data points. The adjusted application rate was then used to define TTR levels by scaling the available TTR data as appropriate.

In order to calculate airborne concentrations from ULV truck fogger applications, EPA used the 2012 Residential SOPs for Outdoor Fogging/Misting Systems, with minimal modification to the well-mixed box (WMB) model. The WMB model allows for the estimation of air concentrations in the breathing zones of adults and children for use in calculating the post-application inhalation exposure to individuals residing in areas being treated by ground application of chlorpyrifos. This methodology is a modification of the previous method used in the 2011 occupational and residential exposure assessment to evaluate post-application inhalation exposure resulting from truck mounted mosquito fogger. The revised methodology more accurately accounts for dilution.

*Combining Residential Exposure and Risk Estimates.* Since dermal, incidental oral, and inhalation exposure routes share a common toxicological endpoint, RBC AChE inhibition risk estimates have been combined for those routes. The incidental oral scenarios (*i.e.,* hand-to-mouth, object-to-mouth, and soil ingestion) should be considered inter-related, as it is likely that these exposures are interspersed over time and are not each occurring simultaneously. Combining all three of these scenarios with the dermal and inhalation exposure scenarios would be unrealistic because of the conservative nature of each individual assessment. Therefore, the post-application exposure scenarios that were combined for children 1 <2 years old are the dermal, inhalation, and hand-to-mouth scenarios (the highest incidental oral exposure expected). This combination should be considered a protective estimate of children's exposure to pesticides.

*Summary of Residential Post-application Non-Cancer Exposure and Risk Estimates.* The assessment of steady state golfer post-application exposures (dermal only) to chlorpyrifos treated turf for the lifestages adults, children 6 to <11 years old, and youths 11 to <16 years old, results in no risks of concern (*i.e.,* children 6 to <11 and youths 11 to <16 years old, MOEs are ≥40; adults, MOEs are ≥100). For the assessment of post-application exposures from public health mosquitocide applications, no combined risks of concern were identified for adults (dermal and inhalation) and children 1 to <2 years old (dermal, incidental oral, and inhalation). A summary of risk estimates is presented in Table 4.

TABLE 4—RESIDENTIAL POST-APPLICATION NON-CANCER EXPOSURE AND RISK ESTIMATES FOR CHLORPYRIFOS

| Lifestage | Post-application exposure scenario | | Application rate [1] | State (TTR data) | Dose (mg/kg/day) [3] | MOEs [4] | Combined routes [5] | Combined MOEs [6] |
|---|---|---|---|---|---|---|---|---|
| | Use site | Route of exposure | | | | | | |
| Adult (Females) | Golf Course Turf | Dermal | 1.0 (Emulsifiable Concentrate). | CA | 0.010 | 1,400 | NA | NA |
| | | | | IN | 0.0069 | 2,100 | | |
| | | | | MS | 0.012 | 1,200 | | |
| | | | | Mean | 0.0095 | 1,500 | | |
| Youths 11 to <16 yrs old. | | | | CA | 0.010 | 1,600 | | |
| | | | | IN | 0.0069 | 2,300 | | |
| | | | | MS | 0.012 | 1,400 | | |
| | | | | Mean | 0.0096 | 1,700 | | |
| Children 6 to <11 years old. | | | | CA | 0.012 | 2,100 | | |
| | | | | IN | 0.0082 | 3,100 | | |
| | | | | MS | 0.014 | 1,800 | | |
| | | | | Mean | 0.011 | 2,200 | | |
| Adult (Females) | | | 1.0 (Granular) | CA | 0.0088 | 1,600 | | |
| Youths 11 to <16 yrs old. | | | | | 0.0088 | 1,900 | | |
| Children 6 to <11 years old. | | | | | 0.010 | 2,400 | | |
| Adult (Females) | Aerial and Ground Based ULV Mosquitocide Applications. | Dermal | 0.010 (Aerial) | MS | 0.00052 | 75,000 | X | 9,100 |
| | | Inhalation | | NA | 0.00060 (mg/m$^3$) | 10,300 | X | |
| Children 1 to <2 yrs old. | Mosquitocide Applications. | Dermal | | MS | 0.00088 | 210,000 | X | 2,300 |
| | | Inhalation | | NA [2] | 0.00060 (mg/m$^3$) | 4,000 | X | |

TABLE 4—RESIDENTIAL POST-APPLICATION NON-CANCER EXPOSURE AND RISK ESTIMATES FOR CHLORPYRIFOS—Continued

| Lifestage | Post-application exposure scenario | | Application rate [1] | State (TTR data) | Dose (mg/kg/day) [3] | MOEs [4] | Combined routes [5] | Combined MOEs [6] |
|---|---|---|---|---|---|---|---|---|
| | Use site | Route of exposure | | | | | | |
| | | Hand-to-Mouth | | MS | 0.000018 | 5,600 | X | |
| | | Object-to-Mouth | | MS | $5.5 \times 10^{-7}$ | 180,000 | NA | NA |
| | | Soil Ingestion | | NA [2] | $1.2 \times 10^{-7}$ | 4,900,000 | NA | NA |
| Adult (Females) | | Dermal | 0.010 (Ground) | MS | 0.000074 | 520,000 | X | 1,200 |
| | | Inhalation | | NA | 0.0051 ($mg/m^3$) | 1,200 | X | |
| Children 1 to <2 yrs | | Dermal | | MS | 0.00013 | 1,500,000 | X | 460 |
| old. | | Inhalation | | NA | 0.0051 ($mg/m^3$) | 460 | X | |
| | | Hand-to-Mouth | | MS | $2.6 \times 10^{-6}$ | 39,000 | X | |
| | | Object-to-Mouth | | MS | $7.9 \times 10^{-8}$ | 1,300,000 | NA | NA |
| | | Soil Ingestion | | NA [2] | $1.7 \times 10^{-8}$ | 34,000,000 | NA | NA |

[1] Based on the maximum application rates registered for golf course turf and ULV mosquito adulticide uses.

[2] The airborne concentrations of chlorpyrifos following ULV mosquito adulticide applications was determined with use of the AgDISP (v8.2.6) model.

[3] Dose (mg/kg/day) equations for golfing and mosquitocide applications are provided in Appendices B and C (Ref. 1) of the updated occupational and residential exposures assessment. For calculation of doses (*i.e.,* dermal, hand-to-mouth, and object-to-mouth) from exposure to ULV mosquito adulticide, TTR data was used. The MS TTR data was selected for use because it is the worst case and, as a result, most protective of human health. Additionally, the fraction of chlorpyrifos residue deposited following mosquitocide application, 35% (0.35), was determined with use of the AgDISP (v8.2.6) model and used for dose calculation. The fraction of chlorpyrifos deposited following ground ULV application, 5% (0.050), is based on surrogate exposure data (malathion). For dose estimation from exposures to golfing on treated turf, on the TTR data was used. Doses have been presented for all State sites, including the mean of all State sites.

[4] MOE = PoD (mg/kg/day) ÷ Dose (mg/kg/day).

[5] X indicates the exposure scenario is included in the combined MOE; NA = Not applicable.

[6] Combined MOE = 1 ÷ (1/dermal MOE) + (1/inhalation MOE) + (1/incidental oral MOE), where applicable.

*v. Aggregating exposures and developing the drinking water level of concern.* Consistent with FFDCA section 408(b)(2)(D)(vi), EPA considers and aggregates (adds) pesticide 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, or the risks themselves can be aggregated. The durations of exposure identified for chlorpyrifos uses are acute and steady state. The acute aggregate assessment includes high end exposure values for food and drinking water but does not include residential exposure estimates. The steady state aggregate assessment includes food, drinking water, and residential exposures and for chlorpyrifos it is protective of the acute aggregate risks because examination indicates it results in higher risk estimates for all situations—so in effect acute residential exposures have also been considered in the aggregate risk assessment process.

For purposes of this proposed rule, EPA is using a DWLOC approach to aggregate risk. Under this approach, EPA calculates the amount of exposure available in the total 'risk cup' for chlorpyrifos oxon in drinking water after accounting for any chlorpyrifos exposures from food and/or residential use.

The DWLOC approach for this proposed rule uses a reciprocal MOE calculation method for adults (females of childbearing age) since the target MOEs are the same for all relevant sources of exposure, *i.e.,* 100X for residential dermal and for dietary food and water. This entails calculating the MOE for water (MOEwater) by deducting the contributions from food (MOEfood) and residential dermal exposure (MOEdermal) from the aggregate MOE (MOEagg) of 100. The aggregate MOE value is the same as target MOE (level of concern). The DWLOC is then calculated by dividing the PoDwater by the MOEwater. The general reciprocal MOE formula is as follows:

MOEagg = 1/((1/MOEwater) + (1/MOEfood) + (1/MOEdermal))

MOEwater = 1/((1/MOEagg) − ((1/MOEfood) + (1/MOEdermal)))

DWLOC= PoDwater/MOEwater

When target MOEs (levels of concern) are not the same across the relevant sources of exposure, the reciprocal MOE approach for calculating DWLOCs is not appropriate; instead an aggregate risk index (ARI) method is used. For purposes of this proposed rule, EPA therefore employed the ARI method for infants, children, and youths because the target MOEs for the relevant sources of exposure are not the same *i.e.,* the target MOE for dietary food and for residential dermal exposures is 40X while the target MOE for drinking water exposure is 50X. In this approach, the aggregate, or 'total', ARI value is assigned as 1 (EPA is generally concerned when any calculated ARIs are less than 1). Similar to the reciprocal MOE approach, the ARIs for food and dermal are deducted from the aggregate ARI to determine the ARI for water. The water ARI is multiplied by the target MOE for water to determine the calculated water MOE (MOEwater). The DWLOC is then calculated by dividing the PoDwater by the MOEwater. The general ARI method formula is as follows:

ARIs for food or dermal are calculated as ARIfood or dermal = (MOEfood or dermal)/(MOEtarget for food or dermal)).

ARIagg = 1/((1/ARIwater) + (1/ARIfood) + (1/ARIdermal))

ARIwater = 1/((1/ARIagg) − ((1/ARIfood) + (1/ARIdermal))); Where ARIagg = 1

MOEwater = ARIwater × MOEtarget.

DWLOC = PoDwater/MOEwater

*Determination of Acute DWLOC.* The acute aggregate assessment includes only food and drinking water. The acute DWLOCs were calculated for infants, children, youths, and adults and are presented in Table 5. The lowest acute DWLOC calculated was for infants (<1 year old) at 24 ppb. Acute exposures greater than 24 ppb are generally considered a risk concern and unsafe for purposes of FFDCA section 408(b).

TABLE 5—ACUTE AGGREGATE (FOOD AND DRINKING WATER) CALCULATION OF DWLOCS [1] [2]

| Population | Food exposure (chlorpyrifos) [3] | | Drinking water exposure (chlorpyrifos) [4] | | Acute DWLOC [5] (ppb chlorpyrifos oxon) |
|---|---|---|---|---|---|
| | MOE | ARI | MOE | ARI | |
| Infants [1] (<1 yr) | 2200 | 55 | 50 | 1.0 | 24 |
| Children [1] (1–2 yrs) | 1400 | 35 | 50 | 1.0 | 60 |
| Youths [1] (6–12 yrs) | 2800 | 70 | 50 | 1.0 | 150 |
| Adults [2] (Females 13–49 yrs) | 3100 | NA | 100 | NA | 53 |

[1] DWLOCs for infants, children and youths are calculated using the ARI (Aggregate Risk Index) approach since target MOEs are different for drinking water (chlorpyrifos oxon target MOE = 50) and for food and residential (chlorpyrifos target MOE = 40) exposure.
[2] DWLOCs for adults (females 13–49 years) are calculated using the reciprocal MOE approach since the target MOEs are the same for drinking water (chlorpyrifos oxon target MOE = 100) and for food and residential (chlorpyrifos target MOE = 100) exposure.
[3] FOOD: MOEfood = PoDfood (ug/kg/day) (from Table 4.8.4)/Food Exposure (ug/kg/day) (from Table 5.4.3). ARIfood = ((MOEfood)/(MOEtarget)).
[4] WATER (ARI approach): ARIwater = 1/((1/ARIagg) − ((1/ARIfood) + (1/ARIdermal))); Where ARIagg = 1 (Note: EPA is generally concerned when calculated ARIs are less than 1). MOEwater = ARIwater × MOEtarget. WATER (Reciprocal MOE approach): MOEwater = 1/((1/MOEagg) − ((1/MOEfood) + (1/MOEdermal))); Where MOEagg =Target MOE.
[5] DWLOC: DWLOC ppb = PoDwater (ppb; from Table 4.8.4)/MOEwater.

*Determination of Steady State DWLOC.* The steady state aggregate assessment includes dietary exposures from food and drinking water and dermal exposures from residential uses (dermal exposures represent the highest residential exposures). The steady state DWLOCs were calculated for infants, children, youths, and adults and are presented in Table 6. The lowest steady state DWLOC calculated was for infants (<1 year old) at 3.9 ppb. Exposures to chlorpyrifos oxon in drinking water at levels that exceed the steady state DWLOC of 3.9 ppb are therefore a risk concern and are considered unsafe for purposes of FFDCA section 408(b).

TABLE 6—STEADY STATE AGGREGATE (FOOD, DRINKING WATER, RESIDENTIAL) CALCULATION OF DWLOCS [1] [2]

| Population | Food exposure (chlorpyrifos) [3] | | Dermal exposure (chlorpyrifos) [4] | | Drinking water exposure (chlorpyrifos oxon) [5] | | Steady state DWLOC [6] (ppb chlorpyrifos oxon) |
|---|---|---|---|---|---|---|---|
| | MOE | ARI | MOE | ARI | MOE | ARI | |
| Infants [1] (<1 yr) | 550 | 14 | NA | NA | 55 | 1.1 | 3.9 |
| Children [1] (1–2 yrs) | 410 | 10 | NA | NA | 55 | 1.1 | 10 |
| Youths [1] (6–12 yrs) | 700 | 18 | 1800 | 45 | 55 | 1.1 | 16 |
| Adults [2] (Females 13–49 yrs) | 1000 | NA | 1200 | NA | 120 | NA | 7.8 |

[1] DWLOCs for infants, children and youths are calculated using the ARI (Aggregate Risk Index) approach since target MOEs are different for drinking water (chlorpyrifos oxon target MOE = 50) and for food and residential (chlorpyrifos target MOE = 40) exposure.
[2] DWLOCs for adults (females 13–49 years) are calculated using the reciprocal MOE approach since the target MOEs are the same for drinking water (chlorpyrifos oxon target MOE = 100) and for food and residential (chlorpyrifos target MOE = 100) exposure.
[3] FOOD: MOEfood = PoDfood (ug/kg/day) (from Table 4.8.4)/Food Exposure (ug/kg/day) (from Table 5.4.4). ARIfood = ((MOEfood)/(MOEtarget)).
[4] DERMAL: MOEdermal = PoDdermal (ug/kg/day) (from Table 4.8.4)/Dermal Exposure (ug/kg/day) (from Table 6.2). ARIdermal = ((MOE dermal)/(MOEtarget)).
[5] WATER (ARI approach): ARIwater = 1/((1/ARIagg) − ((1/ARIfood) + (1/ARIdermal))); Where ARIagg = 1 (Note: EPA is generally concerned when calculated ARIs are less than 1). MOEwater = ARIwater × MOEtarget. WATER (Reciprocal MOE approach): MOEwater = 1/((1/MOEagg) − ((1/MOEfood) + (1/MOEdermal))); Where MOEagg = Target MOE.
[6] DWLOC: DWLOC ppb = PoDwater (ppb; from Table 4.8.4)/MOEwater.

*vi. Estimating aggregate riskÐ comparing DWLOCs to estimated drinking water concentrations.* In a DWLOC aggregate risk assessment, the calculated DWLOC is compared to the EDWC. When the EDWC is less than the DWLOC, there are no risk concerns for exposures to the pesticide in drinking water. Conversely, when the EDWC is greater than the DWLOC, there may be a risk concern. For chlorpyrifos, DWLOCs were calculated for both the acute and steady state aggregate assessments for infants, children, youths and adult females. However, for the national screening level drinking water assessment, only the steady state DWLOCs were compared to the modeled EDWCs (based on a national screen). The calculated steady state DWLOCs are much lower than those for the acute. For example, for infants, the lowest acute DWLOC is 24 ppb while the lowest steady state DWLOC is 3.9 ppb (Tables 5 and 6). Since the lowest DWLOC calculated for any duration or population was the 3.9 ppb steady state exposure value (infants), it is the concentration used for comparison to EPA's modeled EDWCs. Drinking water concentrations of chlorpyrifos oxon above 3.9 ppb may therefore be unsafe. Were EPA to conduct further analyses that compared all acute exposures to EDWC, it is possible that for some limited numbers of use scenarios, the EDWC could result in an exceedance of the acute DWLOC, but not the steady state DWLOC. However, because EPA is proposing to revoke all tolerances based on the steady state DWLOC, it is unnecessary to address that issue at this time.

*EDWCs in Groundwater and Surface Water.* EPA conducted a national screening level drinking water assessment for both groundwater and surface water, with focus on the agricultural uses. For both assessments, EPA calculated EDWCs for chlorpyrifos and chlorpyrifos oxon. Chlorpyrifos

EDWCs were multiplied by 0.9541 (molecular weight correction factor) and 100% (maximum conversion during water purification) to generate chlorpyrifos oxon EDWCs. EPA used a 100% conversion factor for the oxidation of chlorpyrifos to chlorpyrifos oxon as an approximation based on empirical bench scale laboratory data that indicate chlorpyrifos rapidly oxidizes to form chlorpyrifos oxon almost completely during typical water treatment (chlorination). (Ref. 77). There are limited data available on the removal efficiency of chlorpyrifos prior to oxidation or the removal efficiency of chlorpyrifos oxon during the drinking water treatment process. Based on community water systems survey showing that more than 75 percent of community water systems use chlorination to disinfect drinking water in the United States (Ref. 78), the assumption of exposure to chlorpyrifos oxon equivalent to 100% conversion of chlorpyrifos is not considered overly conservative. 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) could reduce the amount of chlorpyrifos oxon in finished drinking water; however, these treatment methods are not typical practices across the country for surface water.

While there is the potential to have both chlorpyrifos and chlorpyrifos oxon present in finished drinking water, no information is available to readily quantify how much of each form remains in the finished water. In the absence of available information, EPA conservatively assumes that 100% of chlorpyrifos that enters a drinking water treatment facility exists after treatment and that during treatment 100% of it converts to chlorpyrifos oxon.

Although chlorpyrifos oxon has a hydrolysis half-life of 5 days, the drinking water treatment simulation half-life for chlorpyrifos oxon is approximately 12 days. (Refs. 79, 80, and 81). Hydrolysis of chlorpyrifos oxon under simulated drinking water treatment processes is slower when compared to hydrolysis of chlorpyrifos oxon in water only; thus, the use of a half-life of 12 days under simulation. Therefore, once chlorpyrifos oxon forms during treatment, little transformation is expected to occur before consumption (during drinking water distribution). There are a wide range of treatment processes and sequences of treatment processes employed at community water systems across the country and there are limited data available on a community-water-system-specific basis to assess the removal or transformation of chlorpyrifos during treatment. These processes are not specifically designed to remove pesticides and pesticide transformation products including chlorpyrifos and chlorpyrifos oxon. In general, drinking water treatment processes, with the exception of activated carbon (Ref. 82), have been shown to have little impact on removal of conventional pesticides.

To illustrate the range of EDWC, two maximum label rate application scenarios were selected to represent high and low end exposures, *i.e.,* tart cherries at 5 applications totaling 14.5 pounds per acre per year, and bulb onions at a single application of one pound per acre per year, respectively. To estimate groundwater EDWCs for chlorpyrifos and chlorpyrifos oxon, EPA conducted a conservative Tier I assessment using SCI–GROW (Screening Concentration in Groundwater, version 2.3, August 8, 2003) and PRZM-Groundwater (PRZM–GW version 1.0, December 11, 2012), using the GW–GUI (Graphical User Interface, version 1.0, December 11, 2012). (Ref. 83). For this assessment, EPA used the results from the model (either SCI–GROW or PRZM–GW) that provided the highest EDWCs. Despite the conservative assumptions used in the Tier I models, as presented below in Table 7 estimated groundwater EDWCs are well below the DWLOCs and therefore do not represent a risk concern.

To calculate the national screening level surface water EDWCs for chlorpyrifos and chlorpyrifos oxon, EPA used the Tier II Surface Water Concentration Calculator (SWCC) version 1.106. The SWCC uses PRZM version 5.0+ (PRZM5) and the Variable Volume Water Body Model (VVWM). PRZM is used to simulate pesticide transport as a result of runoff and erosion from an agricultural field. VVWM estimates environmental fate and transport of pesticides in surface water. For the national screen, upper and lower bound exposure scenarios for surface water were modeled using the highest application rate (tart cherries), and the lowest application rate (bulb onions). This analysis showed that even with only one application, several chlorpyrifos uses may exceed the DWLOC at rates lower than maximum labeled rates (both single as well as yearly), including an application rate of one pound per acre per year. The analysis also showed that the DWLOC exceedances are not expected to be uniformly distributed across the country. The application of chlorpyrifos to tart cherries in Michigan resulted in concentrations that exceeded the drinking water level of concern (DWLOC); whereas, chlorpyrifos applications to bulb onions in Georgia resulted in concentrations below the DWLOC. To investigate with more specificity whether other chlorpyrifos application scenarios may result in concentrations that exceed the DWLOC, a screen (A risk assessment screen is a procedure designed to quickly separate out pesticides uses patterns that meet the safety standard from those that may not meet the safety standard) of all available surface water modeling scenarios was completed considering three different application dates and a single application at several different application rates that ranged from one to six pounds.

EPA also conducted a refined, but limited analysis of the spatial distribution of EDWCs at a regional level and at the drinking water intake level. This exercise demonstrated that chlorpyrifos applications will result in variable drinking water exposures that are highly localized, with concentrations of concern generally occurring in small watersheds where there is a high percent cropped area where chlorpyrifos use is expected.

Finally, EDWCs were also compared to monitoring data. This analysis showed that when modeling scenarios are parameterized to reflect reported use and EDWCs are adjusted to reflect percent cropped area, the EDWCs are within a range of 10x of the measured concentrations reported in the monitoring data. In addition, evaluation of the monitoring data further illustrates that exposures are highly localized. EPA is currently conducting a broader refined assessment that examines EDWCs on a regional and/or watershed scale to pin-point community drinking water systems where exposure to chlorpyrifos oxon as a result of chlorpyrifos applications may pose an exposure concern. As a result of the *PANNA* decision ordering EPA to respond to the PANNA–NRDC Petition by October 31, 2015, EPA has not been able to complete that assessment in advance of this proposed rule. EPA is continuing that assessment and will update this action with the results of that assessment, as warranted.

*Estimated Aggregate RiskÐNational Drinking Water Screen Results.* To determine whether the EDWC exceeds the steady state DWLOC of 3.9 ppb, as noted above, EPA initially conducted a bounding estimate of exposure using a screening level national assessment approach. The results of that exercise are reported in Table 7 for Tier I groundwater and Tier II surface water model simulations.

TABLE 7—ESTIMATED DRINKING WATER CONCENTRATIONS RESULTING FROM THE USE OF CHLORPYRIFOS

| Residue | Surface water | | | | Groundwater |
|---|---|---|---|---|---|
| | 1-in-10 Year peak concentration ppb | 21-Day average concentration ppb | 1-in-10 Year annual average concentration ppb | 30 Year annual average concentration ppb | SCI–GROW Tier I concentration ppb |
| **Michigan Tart Cherries** | | | | | |
| Chlorpyrifos | 129 | 83.8 | 39.2 | 29.7 | 0.16 |
| Chlorpyrifos-oxon | 123 | 80.0 | 37.4 | 28.3 | 0.15 |
| **Georgia Onion** | | | | | |
| Chlorpyrifos | 6.2 | 3.1 | 1.2 | 0.8 | 0.01 |
| Chlorpyrifos-oxon | 5.9 | 3.0 | 1.1 | 0.8 | 0.01 |

SCI–GROW resulted in higher EDWCs than PRZM–GW simulations.

As Table 7 makes clear, the surface water EDWCs for the high application rate Michigan tart cherry scenario significantly exceed the steady state DWLOC of 3.9 ppb for chlorpyrifos oxon, while the low application rate Georgia bulb onion scenario results in EDWC below the DWLOC. Given that the results of the initial bounding estimate showed these mixed results, EPA conducted a further evaluation of additional use scenarios to determine which chlorpyrifos uses do and do not exceed the DWLOC, based on a single application of chlorpyrifos per year at 1 and 4 pounds (where permitted by labeling) of chlorpyrifos per acre. The results for 1 and 4 pounds per acre are reported here as a representation of what EPA believes to be the range of likely chlorpyrifos applications, bearing in mind that chlorpyrifos can be applied at lower and higher single rates (*e.g.,* an application rate of 6 pounds per acre on citrus). This analysis showed that the current maximum application rate scenarios, as well as maximum single application rates for a wide range of chlorpyrifos use scenarios, may result in a 21-day average concentration that exceeds the DWLOC. Table 8 represents the use scenarios that resulted in exceedances of the DWLOC from a single application to the crop and it shows the estimated percentage of 21-day intervals over a 30-year period for which the average concentration is expected to exceed the DWLOC.

TABLE 8—NATIONAL SCREENING RESULTS USING DWLOC APPROACH—SCENARIO REPRESENTATION AND LABELED RATE COMPARISON FOR EXAMPLE USES THAT EXCEED THE DWLOC

| Scenario | Highest 21-day average concentration ppb (application date) | 21-Day exceedance count | Represented use site examples (maximum single application rate) |
|---|---|---|---|
| | | Percent [a] | |
| **1 lb a.i./A** | | | |
| MScornSTD | 16.5 at 1.0 lb a.i./A | 21 | Corn [2 lb a.i./A (aerial and ground)]. |
| TXcornOP | 13.9 at 1.0 lb a.i./A | 13 | Soybean [1 lb a.i./A (aerial); 2.2 (ground)]. |
| ILcornSTD | 14.6 at 1.0 lb a.i./A | 16 | |
| MScotton | 19.8 at 1.0 lb a.i./A [e] | 16 | Cotton [1 lb a.i./A (foliar aerial and ground); seed treatment |
| NCcotton | 14.4 at 1.0 lb a.i./A | 25 | permitted at 2.2 lb a.i./A]. |
| TXcotton | 15.1 at 1.0 lb a.i./A | 8 | |
| NYgrape | 15.7 at 1.0 lb a.i./A | 27 | Grape [2.25 lab a.i./A (ground)]. |
| TXsorghumOP | 25.8 at 1.0 lb a.i./A | 12 | Wheat [1 lb a.i./A (aerial and ground)]. |
| | | | Sunflower [2 lb a.i./A (aerial and ground)]. |
| TXwheatOP | 21.0 at 1.0 lb a.i./A | 6 | *Other Grains:* |
| | | | Sorghum [3.3 lb a.i./A (granular) [b]]. |
| | | | Alfalfa [1 lb a.i./A (aerial and ground)]. |
| PAVegetableNMC | 21.1 at 1.0 lb a.i./A | 18 | Vegetables and Ground Fruit: |
| | | | Strawberry [2 lb a.i./A (aerial and ground)]. |
| | | | Radish [3 lb a.i./A (ground) [d]]. |
| | | | Pepper [1 lb a.i./A (ground)] Onion [1 lb a.i./A (ground)]. |
| CAlettuce | 12.8 at 1.0 lb a.i./A | 8 | |
| MEpotato | 10.7 at 1.0 lb a.i./A | 17 | *Other Row Crops:* |
| NCsweetpotatoSTD | 13.5at 1.0 lb a.i./A | 9 | Tobacco [2 lb a.i./A (aerial and ground)]. |
| | | | Sugarbeets [2 lb a.i./A (granular) [b]]. |
| | | | Peanuts [4 lb a.i./A (granular) [c]] Sweet Potato [2 lb a.i./A (aerial and ground)]. |
| **2 lb a.i./A** | | | |
| MIcherriesSTD | 19.6 at 2.0 lb a.i./A | 42 | Orchards and Vineyards (Tree fruit and Nuts): |
| GApecansSTD | 20.7 at 2.0 lb a.i./A | 12 | Fruit and Nuts [4 lb a.i./A (ground)]. |
| | | | Pecans [2 lb a.i./A (air); 4.3 (ground)]. |

TABLE 8—NATIONAL SCREENING RESULTS USING DWLOC APPROACH—SCENARIO REPRESENTATION AND LABELED RATE COMPARISON FOR EXAMPLE USES THAT EXCEED THE DWLOC—Continued

| Scenario | Highest 21-day average concentration ppb (application date) | 21-Day exceedance count | Represented use site examples (maximum single application rate) |
|---|---|---|---|
| | | Percent [a] | |
| PAapples | 29.1 at 2.0 lb a.i./A | 11 | Apple [2 lb a.i./A (air and ground)].<br>Peach [2 lb a.i./A (air); 3 (ground)]. |
| NCPeanutSTD | 21.0 at 2.0 lb a.i./A | 21 | Peanut:<br>2.0 lb a.i./A (aerial and ground)<br>4 lb a.i./A (granular ground). |
| FLCitrusSTD | 10.1 at 2.0 lb a.i./A | 6 | Citrus:<br>6.0 lb a.i./A [ground including airblast].<br>2.3 lb a.i./A (aerial). |

[a] The highest percent of 21-day time periods where the average concentration exceeds the DWLOC. There are approximately 10,000 21-day time periods per 30 year simulation; however, it should be noted that not all scenarios contain exactly 30 years of weather data.
[b] (1.0 (air and ground)).
[c] (2.0 (air and ground)).
[d] Incorporated or in furrow otherwise (1.0 (air and ground)).
[e] A preplant seed treatment is permitted at 2.2 lb a.i./A and assumes 100% of the applied material washes off the seed coat in the field and is available for transport.

In summary, EPA's analysis shows that the current maximum single application rates for a wide range of chlorpyrifos use scenarios result in a 21-day average concentration that exceeds the DWLOC. And the analysis makes clear that exceedances may occur with considerable frequency.

*Regional Screen.* Although Table 8 makes clear that numerous labeled chlorpyrifos uses result in exceedances of the DWLOC on a national basis, EPA analysis indicates that exposure is likely to be highly localized. While it is currently challenging to assess exposure on a local scale due to the unavailability of data and wide range of characteristics (*e.g.,* environmental characteristics such as soil, weather, etc. or other variables such as drinking water treatment processes) that affect the vulnerability of a given community drinking water system to chlorpyrifos oxon contamination, EPA developed a method to examine the potential geospatial concentration differences for two Hydrological Unit Code (HUC) 2 Regions—HUC 2 Region 17: Pacific Northwest and HUC 2 Region 3: South Atlantic-Gulf, in order to identify use patterns that may result in EDWCs that exceed the DWLOC on a regional basis. (Ref. 84). This analysis considered all potential chlorpyrifos use sites within the HUC 2 regions based on the National Agricultural Statistics Service cropland data layers and survey data. For HUC 2 Region 17, only four chlorpyrifos use patterns were identified as a potential concern based on maximum single application rates of 1 and 4 pounds per acre. However, for HUC 2 Region 3, several chlorpyrifos use scenarios were identified that could exceed the DWLOC, based on the use of available scenarios.

*Watershed Screen.* The uses that exceeded the DWLOC from the regional screening exercise for HUC 2 Region 3 were further explored by utilizing the DWI watershed database. This analysis shows an overlap of potential chlorpyrifos use sites that may result in an exceedance of the DWLOC with watersheds that supply source water for community drinking water systems. In addition, this analysis shows that exposure is not uniform within a HUC 2 Region and that some watersheds are more vulnerable than others. Watershed vulnerability is expected to be greatest for smaller watersheds with high percent cropped areas. Smaller community water systems are generally more vulnerable due to short distribution times and the reliance of chlorination to treat source surface water as well as limited access to other treatment methods such as granular activated carbon.

As noted above, on August 10, 2015, the *PANNA* decision ordered EPA to issue either a proposed or final revocation rule or a full and final response to PANNA–NRDC administrative Petition by October 31, 2015. As a result of that order, EPA is issuing this proposed revocation in advance of completing its refined drinking water assessment. As a result, EPA may update this action with a new or modified drinking water analyses as EPA completes additional work after this proposal.

*Monitoring Data Analysis.* In EPA's PHHRA in 2011, the agency evaluated water monitoring data from the USGS National Water Quality Assessment Program (NAWQA), USEPA/USGS Pilot Reservoir Monitoring Program, USDA PDP, and California Department of Pesticide Regulation (CDPR). The monitoring data showed 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 has detected chlorpyrifos concentrations greater than 1 µg/L in surface water on several occasions, with an observed peak chlorpyrifos concentration of 3.96 µg/L. Sampling frequencies in these monitoring programs were sporadic, however, and generally range from only once per year to twice per month.

Since the preliminary assessment, EPA has evaluated additional water monitoring data from Washington State Department of Ecology and Agriculture (WSDE/WSDA) Cooperative Surface Water Monitoring Program (Refs. 85 and 86), Dow AgroSciences (Ref. 87), and Oregon Department of Environmental Quality. The previously referenced data have also been re-examined to consider short-term exposure (*i.e.,* 21-day average concentrations) considering the importance of the single day exposure and the temporal relationship of exposure. A summary of all surface water monitoring data examined to date for chlorpyrifos are presented in Table 9. Some of the monitoring programs analyzed for chlorpyrifos oxon; however, the number of detections as well as the concentrations were generally much lower. Since the majority of the conversion of chlorpyrifos to chlorpyrifos oxon is

assumed to occur during drinking water treatment, and not in the environment, the monitoring data presented in Table 9 are limited to chlorpyrifos and not its oxon.

TABLE 9—SURFACE WATER MONITORING DATA SUMMARY FOR CHLORPYRIFOS

| Monitoring data | Scale | Years of sampling (number of samples) | Detection frequency (%) | Maximum concentration (µg/L) |
|---|---|---|---|---|
| USGS NAWQA | National | 1991–2012 (30,542) | 15 | 0.57 |
| California Department of Pesticide Regulation. | State | 1991–2012 (13,121) | 20 | 3.96 |
| Washington State Department of Ecology and Agriculture Cooperative Surface Water Monitoring Program. | State | 2003–2013 (4,091) | 8.4 | 0.4 |
| USDA Pesticide Data Program | National | 2004–2009 (raw water; 1,178)<br>2001–2009 (finished water; 2,918). | 0 | na |
| USGS–EPA Pilot Drinking Water Reservoir. | National | 1999–2000 (323) | 5.3 | 0.034 |
| Oregon Department of Environmental Quality. | Watershed (Clackamas) | 2005–2011 (363) | 13 | 2.4 |
| MRID 44711601 (Ref. 87) | Watershed (Orestimba Creek) | 1996–1997 (1,089) | 61 | 2.22 |

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, but are limited for some areas of the United States where chlorpyrifos use occurs. Also, the sampling sites, as well as the number of samples, vary by year. In addition, the vulnerability of the sampling site to chlorpyrifos contamination varies substantially due to use, soil characteristics, weather and agronomic practices. While almost all samples in the monitoring results are below EPA's lowest DWLOC (infant steady state exposures) of 3.9 ppb, none of the monitoring programs examined to date were specifically designed to target chlorpyrifos use (except the Registrant Monitoring Program Ref. 87); therefore, peak concentrations (and likely 21-day average concentrations) of chlorpyrifos and chlorpyrifos oxon likely went undetected in these programs. See Table 9 for a summary of the chlorpyrifos surface water monitoring data.

As a general matter, sampling frequency needs to be approximately equal to the duration of exposure concern. (Ref. 88). The chlorpyrifos monitoring data evaluated thus far also show that as sample frequency increases, so does the detection frequency. This is evident in the registrant-submitted monitoring data, as well as examination of individual sampling sites within the various datasets. The highest detection frequency noted for chlorpyrifos is for Marion Drain (a sample site in Washington), where 103 samples were collected between 2006 and 2008, with 53 chlorpyrifos detections (51%).

Therefore, while there is a large number of individual samples collected and analyzed for chlorpyrifos (or chlorpyrifos oxon) across the United States, it would not be appropriate to combine these data sources to generate exposure estimates or to use these datasets to represent exposure on a national or even regional basis. Thus, comparing the monitoring data results to the DWLOC would not be a reasonable approach for the reasons given above, including limited sample frequency, limited use information, and sampling site variability, on a national or even a regional basis. EPA believes that model estimated concentrations provide more suitable upper bound concentrations for chlorpyrifos and chlorpyrifos oxon.

Additionally, model simulations were completed to represent two different water monitoring datasets—WSDE/WSDA Cooperative Surface Water Monitoring Program (Refs. 85 and 86) and Dow AgroSciences (Ref. 87) Orestimba Creek. For both of these water monitoring programs, enough information was available, including chlorpyrifos use information as well as the PCA, to parameterize the model. In these simulations, the modeled EDWCs were similar to the measured concentrations. This suggests that the modeling results are not overly conservative and supports the use of the model to estimate chlorpyrifos oxon concentrations in drinking water.

As noted above, EPA is continuing to work to refine its drinking water assessment with the goal of pinpointing regions or watersheds where EDWCs may exceed the DWLOC. This effort would include completing the regional assessment presented here for all HUC 2 Regions and crop uses, as well as considering multiple applications per year. Because of the *PANNA* decision ordering EPA to respond to the PANNA–NRDC Petition by October 31, 2015, EPA has not been able to complete this more refined drinking water assessment for chlorpyrifos in advance of this proposed rule. As a result, this proposal does not provide a basis for supporting a more tailored approach to risk mitigation. EPA is continuing to conduct its regional and water-intake level assessment and may update this action with the results of that assessment when it is completed.

*Summary.* EPA's examination of chlorpyrifos agricultural use across the country indicates that there are multiple uses of chlorpyrifos that may result in exposure to chlorpyrifos oxon in finished drinking water at levels that exceed the 21-day steady state DWLOC of 3.9 ppb for infants and children. EPA therefore believes that infants and children in some portions of the country are at some risk from cholinesterase inhibition. While there are uncertainties associated with the model input parameters for which conservative assumptions were made (*e.g.,* one aerobic aquatic metabolism half-life value multiplied by the uncertainty factor of three, stable to hydrolysis, 100% of the cropped watershed is treated, and use of the Index Reservoir as the receiving waterbody), the

modeling is sufficiently representative of some vulnerable water bodies that we cannot make a safety finding based on drinking water exposure. Comparison of model estimated concentrations with measured concentrations suggests that model estimates are consistent with measured concentrations when actual application rates and representative SWCC scenarios are considered and a PCA adjustment factor is applied to the model estimates. This modeling/monitoring comparison suggests that when growers use maximum application rates, or even rates much lower than maximum, chlorpyrifos oxon concentrations in drinking water could pose an exposure concern for a wide range of chlorpyrifos uses. However, these exposures are not expected to be uniformly distributed across the country. As noted, additional analyses are still being conducted in an effort to determine the community water systems where concentrations may be of concern. While that evaluation may ultimately lead to a more tailored approach to risk mitigation, at this point in time, based on the information before EPA, EPA cannot determine that current dietary exposures to chlorpyrifos are safe within the meaning of FFDCA section 408(b)(2)(A). Additionally, although EPA's current assessment indicates that the tolerances for food service and food handling establishments by themselves would not present an unsafe risk (since they do not result in drinking water exposure), because EPA must aggregate all dietary and non-occupational exposures to chlorpyrifos in making a safety finding under the FFDCA, EPA cannot find that any current tolerances are safe and is therefore proposing to revoke all chlorpyrifos tolerances. As noted, however, EPA is soliciting comment on whether it may be possible to retain some group of tolerances.

*vii. Cumulative exposure/risk characterization.* Section 408(b)(2)(D)(v) of the FFDCA provides 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 the pesticide's residues when considered together with other substances that have a common mechanism of toxicity. Chlorpyrifos is a member of the OP class of pesticides, which share AChE inhibition as a common mechanism of toxicity. The agency completed a cumulative risk assessment for OPs in connection with FIFRA reregistration and FFDCA tolerance reassessment (Ref. 10) which can be found on EPA's Web site *http://www.epa.gov/pesticides/cumulative/rraop/.* To the extent that chlorpyrifos tolerances and uses remain following this action, prior to the completion of the FIFRA registration review for chlorpyrifos and the OP class, OPP will update the OP cumulative assessment to ensure that cumulative dietary exposures to the OPs are safe.

*C. When do these actions become effective?*

EPA is proposing that the revocation of the chlorpyrifos tolerances for all commodities become effective 180 days after a final rule is published. The agency believes this revocation date will allow users to exhaust stocks and allow sufficient time for passage of treated commodities through the channels of trade. However, if EPA is presented with information that unused stocks would still be available and that information is verified, the agency will consider extending the expiration date of associated tolerances. If you have comments regarding stocks of remaining chlorpyrifos products and whether the effective date allows sufficient time for treated commodities to clear the channels of trade, please submit comments as described under **SUPPLEMENTARY INFORMATION.**

Any commodities listed in this proposal treated with the pesticides subject to this proposal, and in the channels of trade following the tolerance revocations, shall be subject to FFDCA section 408(1)(5), as established by FQPA. That section provides that, any residues of the subject pesticide in or on such food shall not render the food adulterated so long as it is shown to the satisfaction of the Food and Drug Administration that:

1. The residue is present as the result of an application or use of the pesticide at a time and in a manner that was lawful under FIFRA, and

2. The residue does not exceed the level that was authorized at the time of the application or use to be present on the food under a tolerance or exemption from tolerance. Evidence to show that food was lawfully treated may include records that verify the dates when the pesticide was applied to such food.

## VII. International Residue Limits and Trade Considerations

The tolerance revocations in this proposal are not discriminatory and are designed to ensure that both domestically-produced and imported foods meet the food safety standard established by the FFDCA. The same food safety standards apply to domestically produced and imported foods.

In making its tolerance decisions, EPA seeks to harmonize U.S. tolerances with international standards whenever possible, consistent with U.S. food safety standards and agricultural practices. EPA considers the international maximum residue limits (MRLs) established by the Codex Alimentarius Commission (Codex), as required by FFDCA section 408(b)(4). The Codex Alimentarius is a joint United Nations Food and Agriculture Organization/World Health Organization food standards program, and it is recognized as an international food safety standards-setting organization in trade agreements to which the United States is a party.

EPA also ensures that its tolerance decisions are in keeping with the World Trade Organization's Sanitary and Phytosanitary Measures Agreement. Consistent with that agreement, the effective date EPA is proposing for the revocation of chlorpyrifos tolerances in this proposed rule ensures that the tolerances will remain in effect for a period sufficient to allow a reasonable interval for producers in the exporting countries to adapt to the requirements of these modified tolerances.

## VIII. Statutory and Executive Order Reviews

In this proposed rule, EPA is proposing to revoke specific tolerances established under FFDCA section 408. The Office of Management and Budget (OMB) has exempted this type of action (*e.g.,* tolerance revocation for which extraordinary circumstances do not exist) from review under Executive Order 12866, entitled ''Regulatory Planning and Review'' (58 FR 51735, October 4, 1993). Because this proposed rule has been exempted from review under Executive Order 12866, this proposed rule is not subject to Executive Order 13211, entitled ''Actions Concerning Regulations That Significantly Affect Energy Supply, Distribution, or Use'' (66 FR 28355, May 22, 2001).

This proposed rule does not contain any information collections subject to OMB approval under the Paperwork Reduction Act (PRA) (44 U.S.C. 3501 *et seq.*), or impose any enforceable duty or contain any unfunded mandate as described under Title II of the Unfunded Mandates Reform Act (UMRA) (2 U.S.C. 1501 *et seq.*). Nor does it require any special considerations as required by Executive Order 12898, entitled ''Federal Actions to Address Environmental Justice in Minority Populations and Low-Income

Populations'' (59 FR 7629, February 16, 1994); or OMB review or any other Agency action under Executive Order 13045, entitled ''Protection of Children from Environmental Health Risks and Safety Risks'' (62 FR 19885, April 23, 1997). However, EPA considered the best available science in order to protect children against environmental health risks and this proposed rule is consistent with EPA's 1995 Policy on Evaluating Health Risks to Children (*http://www2.epa.gov/sites/production/files/201405/documents/1995_childrens_health_policy_statement.pdf*), reaffirmed in 2013 (*http://www2.epa.gov/sites/production/files/201405/documents/reaffirmation_memorandum.pdf*).

This proposed rule does not involve any technical standards that would require Agency consideration of voluntary consensus standards pursuant to section 12(d) of the National Technology Transfer and Advancement Act (NTTAA) (15 U.S.C. 272 note). In addition, the Agency has determined that this proposed rule will not have a substantial direct effect on States, on the relationship between the national government and the States, or on the distribution of power and responsibilities among the various levels of government, as specified in Executive Order 13132, entitled ''Federalism'' (64 FR 43255, August 10, 1999). This proposed rule directly regulates growers, food processors, food handlers, and food retailers, not States. This proposed rule does not alter the relationships or distribution of power and responsibilities established by Congress in the preemption provisions of FFDCA section 408(n)(4). For these same reasons, the Agency has determined that this proposed rule does not have any ''tribal implications'' as described in Executive Order 13175, entitled ''Consultation and Coordination with Indian Tribal Governments'' (65 FR 67249, November 9, 2000).

I certify that this action will not have a significant economic impact on a substantial number of small entities under the Regulatory Flexibility Act (RFA), 5 U.S.C. 601 *et seq.* The small entities subject to this proposed action, which directly regulates growers, food processors, food handlers, and food retailers, include small businesses but not small government jurisdiction or small not-for-profit organizations as defined by the RFA.

For purposes of assessing the impacts of this proposed revocation on small businesses, a small business is defined either by the number of employees or by the annual dollar amount of sales/revenues. The level at which an entity is considered small is determined for each NAICS code by the Small Business Administration (SBA). Farms are classified under NAICS code 111, Crop Production, and the SBA defines small entities as farms with total annual sales of $750,000 or less.

Based upon the screening analysis completed (Ref. 89), EPA has determined that less than 39,000 of the 1.2 million small farms nationwide, or approximately 3% of all small farms, may be impacted by this proposed revocation. Of these, 38,000 have potential impacts of less than 1% of gross farm revenue. The analysis indicates that fewer than 1,000 small farms, or 0.1% percent of all small farms, may experience impacts greater than 1%, depending on the availability and cost of alternatives. Based on this analysis, EPA concludes that revoking all tolerances for chlorpyrifos will not have a significant economic impact on a substantial number of small entities. Details of this analysis are presented in EPA's analyses which can be found in the docket (Ref. 89).

## IX. References

EPA has established an official record for this rulemaking. The official record includes all information considered by EPA in developing this proposed rule including documents specifically referenced in this action and listed below, any public comments received during an applicable comment period, and any other information related to this action, including any information claimed as CBI. This official record includes all information physically located in docket ID number EPA–HQ–OPP–2015–0653, any documents identified in this proposal, and documents referenced in documents in the docket. The public version of the official record does not include any information claimed as CBI.


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2. The Petition from NRDC and PANNA and EPA's various responses to it are available in docket number EPA–HQ–OPP–2007–1005 available at *www.regulations.gov.*
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**List of Subjects in 40 CFR Part 180**

Environmental protection, Administrative practice and procedure, Agricultural commodities, Pesticides and pests, Reporting and recordkeeping requirements.

Dated: October 28, 2015.

**Jack E. Housenger,**

*Director, Office of Pesticide Programs.*

Therefore, it is proposed that 40 CFR chapter I be amended as follows:

## PART 180—[AMENDED]

■ 1. The authority citation for part 180 continues to read as follows:

**Authority:** 21 U.S.C. 321(q), 346a and 371.

### § 180.342 [Removed]

■ 2. Remove § 180.342.

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