No. 14-72794

UNITED STATES COURT OF APPEALS
FOR THE NINTH CIRCUIT

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IN RE PESTICIDE ACTION NETWORK NORTH AMERICA
AND
NATURAL RESOURCES DEFENSE COUNCIL, INC.,

Petitioners,

v.

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY,

Respondent.

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# PETITIONERS' MOTION FOR FURTHER MANDAMUS RELIEF

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## INTRODUCTION

On August 10, 2015, this Court issued a writ of mandamus to put an end to respondent Environmental Protection Agency's "egregious" delay in responding to a 2007 petition to revoke all food tolerances and cancel all registrations of chlorpyrifos, a neuro-toxic pesticide. *In re Pesticide Action Network North America v. EPA*, 798 F.3d 809, 811 (9th Cir. 2015). Noting that EPA had "backtracked significantly" from its 2006 finding that chlorpyrifos was safe and had found that a nationwide ban might be justified to protect people from drinking water contamination, the Court held that EPA offered no acceptable justification for further delay and gave EPA until October 31, 2015 to either (1) issue a proposed or final revocation rule, or (2) deny the petition filed by Pesticide Action Network of North America and Natural Resources Defense Council ("PAN/NRDC"). *Id*. at 814-15. In response, EPA proposed to revoke all food tolerances due to drinking water contamination. 80 Fed. Reg. 69,080 (Nov. 6, 2015). In a subsequent order, the Court directed EPA to take final action by December 30, 2016. Order of Dec. 10, 2015 (Dkt. No. 29). When EPA sought an additional six months to conduct further scientific assessments, the Court called the request "another variation on a theme 'of partial reports, missed deadlines, and vague promises of future action' that has been repeated for the past nine years." Order of Aug. 12, 2016 (Dkt. No. 51) (quoting *In re Pesticide Action Network*, 798

F.3d at 811). The Court directed EPA to take final action by March 31, 2017, and made it clear it would not grant any further extensions. *Id*. The Court expressly retained jurisdiction over any further proceedings related to this petition.

Instead of finalizing the proposed revocation order by that deadline, EPA issued an order entitled "Chlorpyrifos: Order Denying PANNA and NRDC's Petition to Revoke Tolerances" ("EPA Response") (Attachment 1). EPA's Response, however, did not make a final determination as to whether chlorpyrifos food tolerances must be revoked. Instead, EPA decided that it preferred to engage in further study of the neuro-developmental harm to children from chlorpyrifos before finalizing the October 2015 proposed revocation rule or taking an alternative regulatory path. *Id*. at 36-37. EPA acknowledged that it had "been unable to persuade the 9th Circuit Court of Appeals that further inquiry into this area of unsettled science should delay EPA's response to the Petition," *id*. at 35, but claimed: "the court's order does not and cannot compel EPA to complete registration review of chlorpyrifos in advance of the October 1, 2022 deadline provided in section 3(g) of FIFRA [Federal Insecticide, Fungicide and Rodenticide Act], 7 U.S.C. § 136a(g)," for completing registration review of pesticides registered prior to 2007. EPA Response at 36.

PAN/NRDC seek further relief from this Court because EPA's response to the petition is no response at all and certainly not what this Court ordered EPA to

do by March 31, 2017. To recap, EPA completed a risk assessment in December 2014, finding unsafe drinking water contamination from chlorpyrifos; it proposed revoking all food tolerances on October 30, 2015 because it could not find that chlorpyrifos is safe; and it reiterated its determination that all chlorpyrifos tolerances had to be revoked based on its updated risk assessment in November 2016 – a risk assessment that found the risks even greater than previously documented. In refusing to act, EPA made no new safety findings, nor could it find chlorpyrifos safe given the extensive scientific record documenting hazards from chlorpyrifos. Because EPA has sidestepped this Court's orders and failed to act on the substance of the petition, PAN/NRDC respectfully ask the Court to grant further mandamus relief, giving EPA 30 days to act on its findings that chlorpyrifos exposures are unsafe and to establish deadlines for the next steps in the revocation and cancellation processes for chlorpyrifos.

## I. EPA'S FINDINGS THAT CHLORPYRIFOS IS NOT SAFE AND THIS COURT'S ORDERS COMPEL IT TO TAKE REGULATORY ACTION NOW, NOT ENGAGE IN FURTHER STUDY.

The Food Quality Protection Act ("FQPA") establishes a precautionary approach to food safety that imposes affirmative obligations on the EPA Administrator to act to prevent unsafe exposures to pesticides. First, the EPA Administrator "may establish or leave in effect a tolerance for a pesticide chemical residue in or on food only if the Administrator determines that the tolerance is safe.

The Administrator shall modify or revoke a tolerance if the Administrator determines it is not safe." 21 U.S.C. § 346a(b)(A)(i). The FQPA's mandates are action-forcing once EPA has made a finding that a pesticide is not safe.[1]

Second, safe "means the Administrator has determined 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." *Id*. § 346a(b)(2)(A)(ii). Scientific uncertainty can preclude a finding that a pesticide is safe, but cannot be a basis for exposing people to potentially unsafe food.

Third, the FQPA directs EPA to act on the basis of available information on the special susceptibility of infants and children, including neurological differences between adults and infants and children, and EPA must apply an additional tenfold margin of safety to account for gaps in data or evidence of pre- or post-natal toxicity to children. *Id*. § 346a(b)(2)(C). Again, Congress directed EPA to act to

[1] In its Response at 28, EPA incorrectly asserts that PAN/NRDC bear the burden of proving that chlorpyrifos is unsafe, but the FQPA places the burden on EPA to find a pesticide is safe. EPA also argues that it need not apply a tenfold FQPA safety factor based on its 2006 risk assessment, even though it has since determined in its 2014 and 2016 risk assessment and proposed tolerance revocations that a tenfold FQPA safety factor is required to protect children from prenatal neuro-developmental harm from chlorpyrifos. EPA Response at 28-30. As this Court recognized, EPA "has backtracked significantly from" its 2006 pronouncement over the last several years. 798 F.3d at 814.

protect children where scientific information shows they are at risk of harm and it will take time to fill in gaps in the data.

For chlorpyrifos, the 2007 petition presented evidence of neuro-developmental harm to children from prenatal exposures, and EPA's 2014 risk assessment found that chlorpyrifos causes harm to children's brains from prenatal exposures and that this harm occurs at exposures far lower than EPA's acute poisoning regulatory endpoint. 2007 Petition (Dkt. No. 1-2); Chlorpyrifos Revised Human Health Risk Assessment for Registration Review (Dec. 29, 2014) ("2014 Risk Assessment") (Dkt. No. 8-2). EPA determined that it had to apply the FQPA tenfold margin of safety to protect children from this harm and that drinking water contamination from chlorpyrifos exposed children to unsafe levels of the pesticide. 2014 Risk Assessment at 48-49, 95-96.

In October 2015, EPA proposed to revoke all tolerances because it could not "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." 80 Fed. Reg. 69,080, 69,081 (Nov. 6, 2015). EPA explained:

> 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 . . . .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.

*Id*.; *see also id*. at 69,106 ("EPA cannot determine that current dietary exposures to chlorpyrifos are safe within the meaning of FFDCA section 408(b)(2)(A)."); *id*. ("EPA cannot find that any current tolerances are safe and is therefore proposing to revoke all chlorpyrifos tolerances."); *accord* Declaration of Richard P. Keigwin, Jr. ¶ 5 (Oct. 29, 2015) (Dkt. No. 25-2) (proposed rule is "based on EPA's conclusion that it could not make the 'reasonable certainty of harm' finding"). Drinking water contamination proved to be the driver for the proposed revocation. 80 Fed. Reg. at 69,083 (drinking water exposures alone "present a risk of concern"); *id*. at 69,097 (aggregate food, residential, and drinking water exposures "do present a significant risk concern and support revocation of all chlorpyrifos tolerances); *id*. at 69,106 (children and infants are at risk from exposures to chlorpyrifos in drinking water and therefore, EPA "cannot make a safety finding based on drinking water exposure.").

EPA based its 2014 risk assessment and its proposal to revoke chlorpyrifos tolerances on acute poisoning risks. In keeping with its policy to protect against the most sensitive health effects and its finding that harm to children's brains occurs at lower doses than EPA's acute poisoning endpoint, EPA conducted another risk assessment using a lower endpoint drawn from studies correlating

chlorpyrifos exposures with such brain impacts as lower IQ, delayed development, and attention deficit disorders. This risk assessment, released in November 2016, revealed even higher and more pervasive risks from chlorpyrifos:

> The revised analysis indicates that expected residues of chlorpyrifos on most individual food crops exceed the ''reasonable certainty of no harm'' safety standard under the Federal Food, Drug, and Cosmetic Act (FFDCA). In addition, the majority of estimated drinking water exposures from currently registered uses, including water exposures from non-food uses, continue to exceed safe levels even taking into account more refined drinking water exposures. Accordingly, based on current labeled uses, the agency's analysis provided in this notice continues to indicate that the risk from the potential aggregate exposure does not meet the FFDCA safety standard. EPA can only retain chlorpyrifos tolerances if it is able to conclude that such tolerances are safe. EPA has not identified a set of currently registered uses that meets the FFDCA safety standard . . . .Further, EPA has not received any proposals for mitigation that registrants may be willing to undertake that would allow the EPA to retain any of the tolerances subject to this rulemaking.

81 Fed. Reg. 81,049, 81,050 (Nov. 17, 2016) (citing Chlorpyrifos Revised Human Health Risk Assessment for Registration Review (Nov. 3, 2016) ("2016 Risk Assessment") (Attachment 2)).

After years of study and several rounds of review by its Scientific Advisory Panel, EPA made an unbroken series of findings that chlorpyrifos harms children's brains at lower exposures than those used by EPA in its previous risk assessments and regulatory decision. As EPA has tried to guard against lower-level exposures associated with the brain damage, its findings of harm from chlorpyrifos have grown in severity. According to its more recent risk assessment, released less than six months ago, people would be harmed from virtually every use and every way

that people are exposed to the pesticide, with children and particularly 1-2 year olds most at risk. 2016 Risk Assessment at 23.

EPA's March 29, 2017 Response is remarkable in its utter silence as to EPA's previous findings. Nowhere does EPA suggest that it has reconsidered its finding that chlorpyrifos is unsafe. Nor does EPA address how it can legally maintain chlorpyrifos tolerances in the face of its findings that chlorpyrifos exposures are unsafe. EPA's only justification for failing to take action in the face of its prior findings that chlorpyrifos exposures are unsafe is its preference to engage in further study and its belief (addressed below) that this Court has not and cannot order it to act before October 2022. EPA has not withdrawn the proposed rule, but has merely decided not to finalize it or take other regulatory action until some unspecified time prior to October 1, 2022. EPA Response at 37. This approach runs counter to EPA's representations to the Court that it would revoke all chlorpyrifos tolerances unless the registrants agreed to mitigation that would ensure the exposures would be safe, *see* EPA Response at 14, or its further assessments showed exposures are at safe levels. Decl. of Jack Housenger in Support of Opposition to Petition for a Writ of Mandamus ¶ 22 n.15 (July 23, 2012) (Dkt. No. 1-2).

This Court has already rejected EPA's pleas for more time to study chlorpyrifos before taking regulatory action. The Court opened its August 2015

Order granting a writ of mandamus, stating: "Although filibustering may be a venerable tradition in the United States Senate, it is frowned upon in administrative agencies tasked with protecting human health." 798 F.3d at 811. EPA had emphasized that the scientific issues are "on the cutting edge of science," involving "novel scientific questions . . . on the frontiers of science." Decl. of Dana Vogel in Support of EPA's Response to Renewed Petition for a Writ of Mandamus ¶ 5 (Dec. 18, 2014) (Dkt. No. 7-2); *see also* Housenger Decl. ¶¶ 11, 15, 24 ("novel questions," "on the edge of evolving science," complex and important scientific issues). In July 2013, this Court denied PAN/NRDC's earlier petition for a writ of mandamus, in part because of the complicated scientific issues. After EPA delayed further, this Court ruled in 2015 that spending nearly a decade reviewing the scientific issues without taking regulatory action was too little, too late. *Compare In re Pesticide Action Network N. Am.*, 532 Fed. Appx. 649, 651 (9th Cir. 2013) *with* 798 F.3d at 811. And in August 2016, this Court refused to allow EPA to delay taking final regulatory action, calling the nine-year delay "objectively extreme" and making it clear that the time for further study had come and gone. Order of August 12, 2016 (Dkt. No. 51).

EPA's March 2017 Response does not determine what regulatory action is required by the FQPA given the brain damage to children from prenatal exposures

to chlorpyrifos.[2] Instead, it presents reasons why EPA will not take final action now, but instead will continue to study the evidence of neuro-developmental harm to children from chlorpyrifos. EPA's Response reads like the earlier declarations and briefs EPA submitted to this Court in opposition to mandamus relief. It recycles EPA's contentions, rejected by this Court, that further study is warranted before EPA could take final action because the scientific issues are novel, highly complex, at the cutting edge of science, and uncertain. EPA Response at 8, 13, 35.[3] EPA admits that it has "been unable to persuade the 9th Circuit Court of Appeals that further inquiry into this area of unsettled science should delay EPA's response to the Petition." *Id*. at 35; *see also id.* at 36 ("As the 9th Circuit has made clear in its August 12, 2016 order in *PANNA v. EPA*, EPA must provide a final response to the Petition by March 31, 2017, regardless of whether the science remains unsettled and irrespective of whatever options may exist for more complete resolution of these issues during the registration review process.").

[2] EPA previously issued partial denials (and one partial grant) of the petition, and the EPA Response finalizes the denials. EPA Response at 15-33. The issues that had not previously been resolved and still remain unresolved are the petition's requests for action to protect children from adverse brain impacts at low doses. On these issues, EPA's Response defers final action pending further study.

[3] EPA asserts that the comments received on the October 2015 proposed rule and its November 2016 renewed findings that chlorpyrifos is not safe suggest continued uncertainty and deep disagreements, without any elaboration. EPA Response at 35. In contrast, earlier in this case, EPA acted with greater specificity on a far more accelerated timetable by informing the Court within 60 days of a comment deadline that it would propose to revoke all chlorpyrifos tolerances. Status Report (June 30, 2015) (Dkt. No. 20).

Recognizing that this Court would not give it an extension to conduct further scientific review, EPA purported to give itself an open-ended extension up to October 1, 2022. It decided to follow its "preference" to explore other scientific approaches to its chlorpyrifos risk assessments and possibly seek peer review before finalizing any regulatory action. *Id*. at 36. EPA's Response states that it is denying the petition, but in reality it is postponing a decision on whether to revoke tolerances to prevent harm to children's brains from prenatal exposures, as the 2007 petition requested. EPA will continue to review the evidence of neuro-developmental harm before "either finalizing the proposed rule of October 30, 2015, or taking an alternative regulatory path." *Id*. at 37.[4]

In its December 10, 2015 Order setting a deadline for final action on the petition, this Court required EPA to demonstrate that extraordinary circumstances made it impracticable to meet the deadline, if it sought an extension. (Dkt. No. 29). When EPA claimed extraordinary circumstances based on its desire to complete additional studies, this Court rebuffed EPA and concluded that "nothing has changed that would justify EPA's continued failure to respond to the pressing

[4] Even though FQPA compels action on tolerances based solely on health risks, EPA's Response at 36 cites the widespread use of chlorpyrifos as undergirding its preference for further study before taking regulatory action, and EPA's press release applauds the decision as welcome news for the farms that use chlorpyrifos. https://www.epa.gov/newsreleases/epa-administrator-pruitt-denies-petition-ban-widely-used-pesticide-0. The fact that chlorpyrifos is widely used or that the agricultural industry may prefer to keep using it is irrelevant to the safety question EPA is required to answer.

human health concerns presented by chlorpyrifos." Order of August 12, 2016 (Dkt. No. 51). The Court acknowledged that the evidence may be imperfect, but concluded that "a claim of premature rulemaking has come and gone," and that further delay is unjustified in light of EPA's history and this Court's rulings. *Id*. By purporting to deny the petition without addressing the merits, EPA is not acting in compliance with this Court's orders or the FQPA's prohibition on the maintenance of tolerances if EPA has found exposures to a pesticide to be unsafe.[5]

## II. THIS COURT POSSESSES AND HAS EXERCISED AUTHORITY TO ORDER EPA TO TAKE REGULATORY ACTION ON CHLORPYRIFOS BEFORE THE OCTOBER 2022 DEADLINE FOR REGISTRATION REVIEW OF OLDER PESTICIDES.

EPA claims that this Court lacks authority to order it to take regulatory action on chlorpyrifos prior to October 1, 2022, the date Congress set for EPA's completion of a comprehensive registration review of all pesticides registered or reregistered prior to October 2007. EPA Response at 36 (Court's order "cannot

[5] Given EPA's disregard of this Court's orders, this is a situation where the Court might choose to issue an order for EPA to show cause why it should not be held in contempt for refusing to follow the Court's orders. *See, e.g., Sierra Club v. Ruckelshaus*, 602 F. Supp. 892, 900-04 (N.D. Cal. 1984) (EPA held in contempt when court rejected argument that EPA was only required to "take final action" and could permissibly withdraw proposed regulations without also finding that a listed hazardous pollutant does not pose a health risk). "A court has the inherent power to punish for civil or criminal contempt any obstruction of justice relating to any judicial proceeding." *Lambert v. Montana*, 545 F.2d 87, 88 (9th Cir. 1976). Civil contempt "consists of a party's disobedience to a specific and definite court order by failure to take all reasonable steps within the party's power to comply." *Reno Air Racing Ass'n, Inc. v. McCord*, 452 F.3d 1126, 1130 (9th Cir. 2006) (internal quotation and citation omitted).

compel EPA to complete the registration review of chlorpyrifos in advance of the October 1, 2022 deadline" for registration review of older pesticides). It claims to have complete discretion to change the priorities and schedules set by the previous administration in the absence of a specific statutory deadline to respond to the petition or complete registration review for chlorpyrifos. *Id*. at 37. In its view, the fact that Congress set a 2022 deadline for completing review of older pesticides deprives this Court of the power to order EPA to act any sooner in response to a petition, even in the face of "objectively extreme" unreasonable delay.

This claim of unbridled discretion ignores the right of citizens to petition their government, including to revoke tolerances, *see* 21 U.S.C. § 346a(d), EPA's statutory obligation to act "within a reasonable time," 5 U.S.C. § 555(b), and this Court's power to issue a writ of mandamus compelling an agency to take action unreasonably delayed. As far back as *Marbury v. Madison*, 5 U.S. 137, 177 (1803), the Supreme Court declared: "It is emphatically the province and duty of the judicial department to say what the law is," and this includes determining when an agency has unreasonably delayed or unlawfully withheld agency action in violation of the Administrative Procedure Act, 5 U.S.C. § 706(1). Not only does this Court have the power to compel an agency to act under the APA and the All Writs Act, 28 U.S.C. § 1651, but it has already exercised that authority in issuing a string of court orders directing EPA to take action to resolve the 2007 petition.

Under those orders, EPA had to make it a priority to address the neuro-developmental harm to children and to meet the court-imposed deadlines.[6]

Not only has this Court exercised its power to compel EPA to take regulatory action by a date certain, but EPA represented to the Court under oath that it was prioritizing chlorpyrifos and working diligently to determine whether the tolerances had to be revoked. The agency relied on its prioritization of chlorpyrifos in registration review to try to convince this Court in 2013 and again in 2015 that it was acting expeditiously to address the mounting evidence of adverse brain impacts to children from prenatal exposures. *See* Housenger Decl. ¶ 13 (EPA moved up chlorpyrifos in registration review because of the scientific issues with it and the other organophosphates and to respond to the petition). EPA

[6] EPA cites *Federal Communications Commission v. Fox Television Stations*, 556 U.S. 502 (2009), for the proposition that it has no obligation to provide a justification for reversing course more substantial than what is needed to adopt a policy in the first instance. *Fox Television*, however, requires agencies to provide a reasoned explanation that comports with *Motor Vehicles Mfrs. Ass'n v. State Farm Mut. Automobile Ins. Co.*, 463 U.S. 43 (1983), and to address prior factual findings and circumstances that underlay the earlier agency decision. 556 U.S. at 515-16. Here, EPA prioritized registration review of chlorpyrifos, originally setting it for completion in 2015, because of the evidence of neurological harm to children and the PAN/NRDC petition. EPA Response at 8, 13. Chlorpyrifos was leading the way by addressing scientific issues that would also be drivers in EPA's review of many other pesticides, including the evidence of neuro-developmental harm, the use of epidemiology studies in pesticide regulation, and protecting children from spray drift and volatilization exposures. Vogel Decl. ¶ 5. Moreover, this Court had little difficulty concluding that EPA should act quickly to resolve the petition in light of the considerable health risks prejudiced by further delay. 798 F.3d at 814; Order of August 12, 2016. EPA must, but has failed to, provide a reasoned justification for disregarding these findings and circumstances.

never contested this Court's power to compel it to take regulatory action on chlorpyrifos. Instead, it defended its slow pace under the well-established factors developed by the courts for deciding whether to exercise that power. *See* EPA's Response to Renewed Petition for Writ of Mandamus at 13, 16-30 (Dkt. No. 7-1) (applying factors established in *Telecomms. Research & Action Ctr. v. FCC*, 750 F.2d 70 (D.C. Cir. 1984)).[7]

EPA is wrong in asserting that this Court lacks the power to compel it to take final regulatory action on chlorpyrifos prior to 2022. This Court unquestionably has the power to issue orders to put an end to EPA's unreasonable delay in taking final regulatory action.

[7] As such, EPA waived the argument that this Court lacks authority to compel it to act to protect children from chlorpyrifos prior to the 2022 registration review deadline. *See Outdoor Media Grp., Inc. v. City of Beaumont*, 506 F.3d 895, 900 (9th Cir. 2007) (arguments that are not raised in a party's opening brief are generally deemed waived by federal courts); Fed. R. App. P. 28(a)(8)(A). EPA did not present this argument in its initial briefing, or at any other time during the course of this litigation, and has thus deprived PAN/NRDC "of a fair opportunity to respond comprehensively to [the] claim," and has deprived this Court "of the benefit of a robust debate informed by zealous advocacy." *City of Beaumont*, 506 F.3d at 900. EPA noted that it was "not required by law to complete another review until 2022," EPA Response to Renewed Petition for Writ of Mandamus at 8, but this statement does not contest the Court's authority to order it to address the chlorpyrifos petition sooner. *See Navajo Nation v. U.S. Forest Serv.*, 535 F.3d 1058, 1079 n.26 (9th Cir. 2008) ("It is well-established that a bare assertion in an appellate brief, with no supporting argument, is insufficient to preserve a claim on appeal."); *Simpson v. Union Oil Co. of Cal.*, 411 F.2d 897, 900 n.2 (9th Cir. 1969), *rev'd on other grounds*, 396 U.S. 13 (1969) (concluding that issues not discussed in briefs are waived despite mention in statement of case or specifications of error).

## III. THE COURT SHOULD ORDER FURTHER RELIEF FOR EACH STEP OF THE REVOCATION AND CANCELLATION PROCESSES.

PAN/NRDC ask the Court to order further relief made necessary by EPA's misinterpretation and disregard of this Court's prior orders. In 2015, this Court determined that EPA's delay was prejudicing considerable human health interests. That prejudice has only worsened with EPA's further delay despite its findings that chlorpyrifos is even more harmful than its 2014 risk assessment demonstrated. Accordingly, PAN/NRDC ask the Court to order the following relief:

1. An order directing EPA to take regulatory action within 30 days on its finding that chlorpyrifos is unsafe.

Given that this Court rejected EPA's plea for a six-month extension of a court-ordered December 30, 2016 deadline for final action and EPA's failure to take the required action by its March 31, 2017 deadline, a further order is warranted giving EPA a short period of time to do what it was required to do by March 31, 2017. Because of EPA's assertion of unbridled authority to re-order priorities and postpone all regulatory action on chlorpyrifos, this Court should make it abundantly clear that what is required within 30 days is final regulatory action based on the neuro-developmental and other risks posed by chlorpyrifos exposures. PAN/NRDC believe the only legally and scientifically defensible action is revocation of all food tolerances and cancellation of all uses as the 2007 petition sought. The only way to avoid revoking the food tolerances and

cancelling the uses would be for EPA to find that chlorpyrifos exposures are safe, but EPA cannot make such a finding in the face of the overwhelming body of scientific evidence, EPA's risk assessments, its representations to this Court, and its findings that chlorpyrifos is not safe.[8]

2. An order requiring EPA to resolve objections to its final regulatory action within 60 days

As EPA's Response explains at 5-6, EPA resolves petitions regarding tolerances through a two-stage process. The first stage consists of the EPA's decision on the petition and ends with publication of that decision in the Federal Register. In the second stage, parties who disagree with EPA's decision, whether a denial or grant of a petition or revocation of tolerances, may file administrative objections with EPA within 60 days of the Federal Register publication. 21 U.S.C. § 346a(g)(2)(A). The objections allow parties to contest the conclusions EPA reached.

Filing objections and awaiting their resolution by the EPA Administrator is a prerequisite to obtaining judicial review. 21 U.S.C. § 346a(h)(1) (within 60 days of EPA's resolution of objections, adversely affected parties may seek review in

[8] The FQPA specifies that a tolerance revocation shall take effect upon publication unless specified otherwise. 21 U.S.C. § 346a(g)(1). As proposed, the tolerance revocation would become effective 180 days after publication of the final rule. 80 Fed. Reg. at 69,106. Given the length of time since the rule was proposed, the Court should direct EPA to make the final revocation rule effective no later than six months after publication, unless EPA demonstrates extraordinary circumstances for a longer compliance timetable.

the court of appeals). The Administrator is to issue a final order resolving the objections "[a]s soon as practicable after receiving the arguments of the parties," but there is no specific statutory deadline for EPA to issue a decision on objections. Given the delay in EPA's resolution of PAN/NRDC's 2007 petition, and EPA's revelation in its March 29, 2017 Response that it prefers to put off regulatory action on chlorpyrifos for more than five additional years, this Court should order EPA to resolve any objections within 60 days of their receipt.[9]

3. An order requiring EPA to issue a notice of intent to cancel all chlorpyrifos uses within 60 days

PAN/NRDC's 2007 petition sought revocation of all chlorpyrifos tolerances and cancellation of all chlorpyrifos registrations under FIFRA. An order revoking tolerances would prohibit residues of chlorpyrifos on food and require cancellation of food uses of the pesticide. 7 U.S.C. § 136(bb)(2) (EPA can maintain a pesticide registration only if there are no unreasonable adverse effects, and that term is defined to include "a human dietary risk from residues that result from a use of a pesticide in or on any food inconsistent with the standard under section 346a of

[9] A party filing objections can seek an evidentiary hearing, but not on issues it could have presented in the first stage of review of a petition. EPA Response at 6; *Nat'l Corn Growers Ass'n v. EPA*, 613 F.3d 266, 272 (2010) (objection stage allows an interested party to challenge a fact, law, or policy that appeared for the first time in the final rule). If EPA grants such a hearing, the Court should require resolution of the hearing and final EPA action on the objections within 120 days. A party could also ask EPA to stay a revocation rule or delay its effective date during the objection process. This Court should prohibit EPA from doing so unless it demonstrates extraordinary circumstances warrant such a delay.

Title 21"). EPA has found drinking water contamination from all chlorpyrifos uses, including nonfood uses, and will need to take regulatory action to end such uses in addition to stopping food uses. PAN/NRDC asks the Court to require EPA to initiate cancellation proceedings within 60 days by issuing a notice of intent to cancel chlorpyrifos uses consistent with its risk assessments and findings that chlorpyrifos is unsafe.

4. An order requiring EPA to file six-month status reports

PAN/NRDC ask the Court to direct EPA to file status reports every six months until it finalizes the tolerance revocation process, including by fully resolving any objections, and completes cancellation proceedings. Such relief is warranted in light of the pattern of missed deadlines and what this Court called "egregious" delay when it issued the writ of mandamus and "objectively extreme" when it later denied EPA a six-month extension for taking final action. 798 F.3d at 811; Order of August 12, 2016 at 4; *see Pub. Citizen Health Research Grp. v. Brock*, 823 F.2d 626, 629 (D.C. Cir. 1987) (ordering agency to adhere to specific schedule and to report to the Court every six months on the progress made).

## CONCLUSION

PAN/NRDC ask the Court to order the further requested relief to ensure EPA takes regulatory action to protect children from a hazardous pesticide in a timely manner.

Dated: April 5, 2017

Respectfully submitted,

*s/ Patti A.Goldman*

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## CERTIFICATE OF SERVICE

I hereby certify that I served the foregoing document(s) on the following party via CM/ECF Service:

1. Petitioners' Motion For Further Mandamus Relief

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*Attorneys for Respondent*

I declare under penalty of perjury that the foregoing is true and correct.

Executed this 5th day of April, 2017, at Seattle, Washington.

*s/ Patti A.Goldman*
PATTI A. GOLDMAN

# ATTACHMENT 1

BILLING CODE 6560-50-P

**ENVIRONMENTAL PROTECTION AGENCY**

**[EPA-HQ-OPP-2007-1005; FRL-9960-77]**

**Chlorpyrifos; Order Denying PANNA and NRDC's Petition to Revoke Tolerances**

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

**ACTION:** Order.

**SUMMARY:** In this Order, EPA denies a petition requesting that EPA revoke all tolerances for the pesticide chlorpyrifos under section 408(d) of the Federal Food, Drug, and Cosmetic Act and cancel all chlorpyrifos registrations under the Federal Insecticide, Fungicide and Rodenticide Act. The petition was filed in September 2007 by the Pesticide Action Network North America (PANNA) and the Natural Resources Defense Council (NRDC).

**DATES:** This Order is effective [*insert date of publication in the **Federal Register***]. Objections and requests for hearings must be received on or before [*insert date 60 days after date of publication in the **Federal Register***], and must be filed in accordance with the instructions provided in 40 CFR part 178 (see also Unit I. of the **SUPPLEMENTARY INFORMATION**.)

**ADDRESSES:** The docket for this action, identified by docket identification (ID) number EPA-HQ-OPP-2007-1005, is available at *http://www.regulations.gov* or at the Office of Pesticide Programs Regulatory Public Docket (OPP Docket) in the Environmental Protection Agency Docket Center (EPA/DC), West William Jefferson Clinton Bldg., Rm. 3334, 1301 Constitution Ave., NW., Washington, DC 20460-0001. The Public Reading Room is open from 8:30 a.m. to 4:30 p.m., Monday through Friday,

excluding legal holidays. The telephone number for the Public Reading Room is (202) 566-1744, and the telephone number for the OPP Docket is (703) 305-5805. Please review the visitor instructions and additional information about the docket available at *http://www.epa.gov/dockets*.

**FOR FURTHER INFORMATION CONTACT:** Pesticide Re-Evaluation Division (7508P), Office of Pesticide Programs, Environmental Protection Agency, 1200 Pennsylvania Ave., NW., Washington, DC 20460-0001; telephone number: (703) 347-0206; email address: *OPPChlorpyrifosInquiries@epa.gov*.

**SUPPLEMENTARY INFORMATION:**

## I. General Information

### *A. Does this Action Apply to Me?*

In this document EPA denies a petition by PANNA and the NRDC to revoke pesticide tolerances and cancel pesticide registrations. This action may also be of interest to agricultural producers, food manufacturers, or pesticide manufacturers. Potentially affected entities may include, but are not limited to those engaged in the following activities:

- Crop production (North American Industrial Classification System (NAICS) code 111), e.g., agricultural workers; greenhouse, nursery, and floriculture workers; farmers.
- Animal production (NAICS code 112), e.g., cattle ranchers and farmers, dairy cattle farmers, livestock farmers.
- Food manufacturing (NAICS code 311), e.g. agricultural workers; farmers; greenhouse, nursery, and floriculture workers; ranchers; pesticide applicators.

- Pesticide manufacturing (NAICS code 32532), e.g. agricultural workers; commercial applicators; farmers, greenhouse, nursery, and floriculture workers; residential users.

This listing is not intended to be exhaustive, but rather to provide a guide for readers regarding entities likely to be affected by this action. Other types of entities not listed in this unit could also be affected. The NAICS codes have been provided to assists you and others in determining whether this action might apply to certain entities. If you have any questions regarding the applicability of this action to a particular entity, consult the person listed under **FOR FURTHER INFORMATION CONTACT**.

*B. How Can I Get Copies of This Document and Other Related Information?*

EPA has established a docket for this action under Docket ID No. EPA-HQ-OPP-2007-1005. Additional information relevant to this action is located in the chlorpyrifos registration review docket under Docket ID No, EPA-HQ-OPP-2008-0850 and the chlorpyrifos tolerance rulemaking docket under Docket ID No, EPA-HQ-OPP-2015-0653. To access the electronic docket, go to *http://www.regulations.gov*, select "Advanced Search," then "Docket Search." Insert the docket ID number where indicated and select the "Submit" button. Follow the instructions on the regulations.gov website to view the docket index or access available documents. All documents in the docket are listed in the docket index available in regulations.gov. Although listed in the index, some information is not publicly available, e.g., Confidential Business Information (CBI) or other information whose disclosure is restricted by statute. Certain other material, such as copyrighted material, is not placed on the Internet and will be publicly available only in hard copy form. Publicly available docket materials are available in the electronic

docket or, if only available in hard copy, at the OPP Regulatory Public Docket in Rm. S-4400, One Potomac Yard (South Bldg.), 2777 S. Crystal Dr., Arlington, VA. The Docket Facility is open from 8:30 a.m. to 4 p.m. Monday through Friday, excluding legal holidays. The Docket Facility telephone number is (703) 305-5805.

*C. Can I File an Objection or Hearing Request?*

Under section 408(g) of the Federal Food, Drug and Cosmetic Act (FFDCA) (21 U.S.C. 346a(g)), any person may file an objection to any aspect of this order and may also request a hearing on those objections. You must file your objection or request a hearing on this order in accordance with the instructions provided in 40 CFR part 178. To ensure proper receipt by EPA, you must identify docket ID number EPA-HQ-OPP-2007-1005 in the subject line on the first page of your submission. All objections and requests for a hearing must be in writing, and must be received by the Hearing Clerk on or before [*insert date 60 days after date of publication in the* **Federal Register**], and may be submitted by one of the following methods:

• *Mail*:. U.S. EPA Office of Administrative Law Judges, Mailcode 1900R**,** 1200 Pennsylvania Ave., NW., Washington, DC 20460

• *Hand Delivery*: U.S. Environmental Protection Agency Office of Administrative Law Judges, Ronald Reagan Building, Rm. M1200, 1300 Pennsylvania Ave., NW., Washington, DC 20004. Deliveries are only accepted during the Office's normal hours of operation (8:30 a.m. to 4 p.m., Monday through Friday, excluding legal holidays). Special arrangements should be made for deliveries of boxed information. The Office's telephone number is (202) 564-6255.

In addition to filing an objection or hearing request with the Hearing Clerk as

described in 40 CFR part 178, please submit a copy of the filing that does not contain CBI for inclusion in the public docket that is described in I.B.1 above. Information not marked confidential pursuant to 40 CFR part 2 may be disclosed publicly by EPA without prior notice. Submit this copy, identified by docket ID number EPA-HQ-OPP-2007-1005, by one of the following methods:

- *Federal eRulemaking Portal*: *http://www.regulations.gov*. Follow the on-line instructions for submitting comments.

- *Mail*: U.S. Environmental Protection Agency Office of Pesticide Programs (OPP) Public Regulatory Docket (7502P), 1200 Pennsylvania, Ave., NW, Washington DC 20460-0001.

- *Delivery*: OPP Regulatory Public Docket (7502P), Environmental Protection Agency, Rm. S-4400, One Potomac Yard (South Bldg.), 2777 S. Crystal Dr., Arlington, VA. Deliveries are only accepted during the Docket's normal hours of operation (8:30 a.m. to 4 p.m., Monday through Friday, excluding legal holidays). Special arrangements should be made for deliveries of boxed information. The Docket Facility telephone number is (703) 305-5805.

*D. What Should be Included in Objections?*

The objection stage is the second stage in the petition process under FFDCA section 408. This multi-stage process is initiated by a petition requesting establishment, modification, or revocation of a tolerance. Once EPA makes a decision on a petition, and publishes its decision in the Federal Register, the second stage of the petition process is triggered. At this point, parties who disagree with EPA's decision, whether it is a decision to grant or deny the petition, may file objections with EPA to the decision made.

The objection stage gives parties a chance to seek review of EPA's decision before the Agency. This is an opportunity for parties to contest the conclusions EPA reached and the determinations underlying those conclusions. As an administrative review stage, it is not an opportunity to raise new issues or arguments or present facts or information that were available earlier. On the other hand, parties must do more than repeat the claims in the petition. The objection stage is the opportunity to challenge EPA's decision on the petition. An objection fails on its face if it does not identify aspects of EPA's decision believed to be in error and explain the reason why EPA's decision is incorrect. This two-stage process insures that issues are fully aired before the Agency and a comprehensive record is compiled, prior to judicial review.

## II. Introduction

### *A. What Action is the Agency Taking?*

In this document, EPA denies a petition by PANNA and the NRDC. In a petition dated September 12, 2007, PANNA and NRDC (the petitioners) requested that EPA revoke all tolerances for the pesticide chlorpyrifos established under section 408 of the FFDCA. (Ref. 1) The petition also sought the cancellation of all chlorpyrifos pesticide product registrations under section 6 the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA), 7 U.S.C. 136d. The PANNA and NRDC petition (the Petition) raised the following claims regarding EPA's reregistration and active registrations of chlorpyrifos in support of the request for tolerance revocation and product cancellation:

1. EPA has ignored genetic evidence of vulnerable populations.
2. EPA has needlessly delayed a decision regarding endocrine disrupting effects.
3. EPA has ignored data regarding cancer risks.

4. EPA's 2006 cumulative risk assessment (CRA) for the organophosphates misrepresented risks and failed to apply FQPA 10X safety factor. [For convenience's sake, the legal requirements regarding the additional safety margin for infants and children in section 408(b)(2)(C) of the FFDCA are referred to throughout this response as the "FQPA 10X safety factor" or simply the "FQPA safety factor." Due to Congress' 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.]

5. EPA has over-relied on registrant data.

6. EPA has failed to properly address the exporting hazard in foreign countries from chlorpyrifos.

7. EPA has failed to quantitatively incorporate data demonstrating long-lasting effects from early life exposure to chlorpyrifos in children.

8. EPA has disregarded data demonstrating that there is no evidence of a safe level of exposure during pre-birth and early life stages.

9. EPA has failed to cite or quantitatively incorporate studies and clinical reports suggesting potential adverse effects below 10% cholinesterase inhibition.

10. EPA has failed to incorporate inhalation routes of exposure.

In this order EPA is denying the Petition in full. EPA provided the petitioners with two interim responses on July 16, 2012, and July 15, 2014, respectively. The July 16, 2012, response denied claim 6 (export hazard) completely and that portion of the response was a final agency action. The remainder of the July 16, 2012, response and the July 15, 2014, response expressed EPA's intention to deny six other petition claims (1-5

and 10). [In the 2012 response, EPA did, however, inform petitioners of its approval of label mitigation (in the form of rate reductions and spray drift buffers) to reduce bystander risks, including risks from inhalation exposure, which in effect partially granted petition claim 10.] EPA made clear in both the 2012 and 2014 responses that, absent a request from petitioners, EPA's denial of those six claims would not be made final until EPA finalized its response to the entire Petition. Petitioners made no such request. EPA is finalizing its denial of those six claims in this order.

The remaining claims (7-9) all related to same issue: whether the potential exists for chlorpyrifos to cause neurodevelopmental effects in children at exposure levels below EPA's existing regulatory standard (10% cholinesterase inhibition). While these claims raised novel, highly complex and unresolved scientific issues, EPA decided it would nonetheless expedite the registration review of chlorpyrifos under FIFRA section 3(g), and attempt to address these issues several years in advance of the October 1, 2022 deadline for completing that review. Accordingly, EPA also decided as a policy matter that it would address the Petition claims raising these matters on a similar timeframe. Although EPA had expedited its registration review to address these issues, the petitioners were not satisfied with EPA's progress in responding to the Petition and they brought legal action in the 9$^{th}$ Circuit Court of Appeals to compel EPA to either issue an order denying the Petition or to grant the Petition by initiating the tolerance revocation process. In August 2015, the 9$^{th}$ Circuit issued a ruling in favor of the petitioners and ordered EPA to respond to the Petition by either denying the Petition or issuing a proposed or final rule revoking chlorpyrifos tolerances. *In re Pesticide Action Network of North America v. EPA*, 798 F.3d (9th Cir. 2015).

On November 6, 2015, pursuant to the 9th Circuit's order, EPA proposed to revoke all chlorpyrifos tolerances based in part on uncertainty surrounding the potential for chlorpyrifos to cause neurodevelopmental effects – the issue raised in petition claims 7-9. Following publication of the proposal, the 9th Circuit announced that it would retain jurisdiction over this matter and on August 12, 2016, the court further ordered EPA to complete a final petition response by March 31, 2017 and made clear that no further extensions would be granted. On November 17, 2016, EPA published a notice of data availability that released for public comment EPA's revised risk assessment that proposed a new regulatory point of departure based on the potential for chlorpyrifos to result in adverse neurodevelopmental effects.

Following a review of comments on both the November 2015 proposal and the November 2016 notice of data availability, EPA has concluded that, despite several years of study, the science addressing neurodevelopmental effects remains unresolved and that further evaluation of the science during the remaining time for completion of registration review is warranted to achieve greater certainty as to whether the potential exists for adverse neurodevelopmental effects to occur from current human exposures to chlorpyrifos. EPA has therefore concluded that it will not complete the human health portion of the registration review or any associated tolerance revocation of chlorpyrifos without first attempting to come to a clearer scientific resolution on those issues. As noted, Congress has provided that EPA must complete registration review by October 1, 2022. Because the 9th Circuit's August 12, 2016 order has made clear, however, that further extensions to the March 31, 2017 deadline for responding to the Petition would not be granted, EPA is today also denying all remaining petition claims.

*B. What Is the Agency's Authority for Taking This Action?*

Under section 408(d)(4) of the FFDCA, EPA is authorized to respond to a section 408(d) petition to revoke tolerance either by issuing a final rule revoking the tolerances, issuing a proposed rule, or issuing an order denying the Petition.

**III. Statutory and Regulatory Background**

*A. FFDCA/FIFRA and Applicable Regulations*

1. *In general*. EPA establishes maximum residue limits, or ''tolerances,'' for pesticide residues in food and feed commodities under section 408 of the FFDCA. Without such a tolerance or an exemption from the requirement of a tolerance, a food containing a pesticide residue is ''adulterated'' under section 402 of the FFDCA and may not be legally moved in interstate commerce. Section 408 was substantially rewritten by the Food Quality Protection Act of 1996 (FQPA) (Public Law 104–170, 110 Stat. 1489 (1996)), which established a detailed safety standard for pesticides and integrated EPA's regulation of pesticide food residues under the FFDCA with EPA's registration and re-evaluation of pesticides under FIFRA. The standard for issuing or maintaining a tolerance under section 408(b)(2)(A)(i) of the FFDCA is whether it is ''safe.'' ''Safe'' is defined by section 408(b)(2)(A)(ii) 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.''

While the FFDCA authorizes the establishment of legal limits for pesticide residues in food, section 3(a) of FIFRA requires the approval of pesticides prior to their

sale and distribution, and establishes a registration regime for regulating the use of pesticides. FIFRA regulates pesticide use in conjunction with its registration scheme by requiring EPA review and approval of pesticide labels and specifying that use of a pesticide inconsistent with its label is a violation of federal law. In the FQPA, Congress integrated action under the two statutes by requiring that the safety standard under the FFDCA be used as a criterion in FIFRA registration actions as to pesticide uses which result in dietary risk from residues in or on food, (*see* FIFRA section 2(bb)), and directing that EPA coordinate, to the extent practicable, revocations of tolerances with pesticide cancellations under FIFRA. (*see* FFDCA section 408(l)(1)). Under section 3(g) of FIFRA, EPA is required to re-evaluate pesticides under the FIFRA standard – which includes a determination regarding the safety of existing FFDCA tolerances – every 15 years under a program known as "registration review." The deadline for completing the registration review for chlorpyrifos is October 1, 2022.

2. *Procedures for establishing, amending, or revoking tolerances*. Tolerances are established, amended, or revoked by rulemaking under the unique procedural framework set forth in the FFDCA. Generally, a tolerance rulemaking is initiated by the party seeking to establish, amend, or revoke a tolerance by means of filing a petition with EPA. (*See* FFDCA section 408(d)(1)). EPA publishes in the **Federal Register** a notice of the petition filing and requests public comment. After reviewing the petition, and any comments received on it, section 408(d)(4) provides that EPA may issue a final rule establishing, amending, or revoking the tolerance, issue a proposed rule to do the same, or deny the petition.

Once EPA takes final action on the petition by establishing, amending, or

revoking the tolerance or denying the petition, section 408(g)(2) allows any party to file objections with EPA and seek an evidentiary hearing on those objections. Objections and hearing requests must be filed within 60 days. Section 408(g)(2)(B) provides that EPA shall ''hold a public evidentiary hearing if and to the extent the Administrator determines that such a public hearing is necessary to receive factual evidence relevant to material issues of fact raised by the objections.'' EPA regulations make clear that hearings will only be granted where it is shown that there is ''a genuine and substantial issue of fact,'' the requestor has identified evidence 'which "would, if established, resolve one or more of such issues in favor of the requestor,'' and the issue is ''determinative'' with regard to the relief requested. (40 CFR 178.32(b)). Further, a party may not raise issues in objections unless they were part of the petition and an objecting party must state objections to the EPA decision and not just repeat the allegations in its petition. *Corn Growers v. EPA*, 613 F.2d 266 (D.C. Cir. 2010), cert. denied, 131 S. Ct. 2931 (2011). EPA's final order on the objections is subject to judicial review. (21 U.S.C. 346a(h)(1)).

**IV. Chlorpyrifos Regulatory Background**

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. By pounds of active ingredient, it is the most widely used conventional insecticide in the country. Currently registered use sites include a large variety of food crops (including tree fruits and nuts, many types of small fruits and vegetables, including vegetable seed treatments, grain/oilseed crops, and cotton, for example), and non-food use settings (e.g., ornamental and agricultural seed production, non-residential turf, industrial sites/rights of way, greenhouse and nursery production,

sod farms, pulpwood production, public health and wood protection). For some of these crops, chlorpyrifos is currently the only cost-effective choice for control of certain insect pests. 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. Having completed reregistration and tolerance reassessment, EPA is required to complete the next re-evaluation of chlorpyrifos under the FIFRA section 3(g) registration review program by October 1, 2022. Given ongoing scientific developments in the study of the OPs generally, in March 2009 EPA announced its decision to prioritize the FIFRA section 3(g) registration review of chlorpyrifos by opening a public docket and releasing a preliminary work plan to complete the chlorpyrifos registration review by 2015 – 7 years in advance of the date required by law.

The registration review of chlorpyrifos and the OPs has presented EPA with numerous novel scientific issues that the agency has taken to multiple FIFRA Scientific Advisory Panel (SAP) meetings since the completion of reregistration. [The SAP is a federal advisory committee created by section 25(d) of FIFRA, that serves as EPA's primary source of peer review for significant regulatory and policy matters involving pesticides.] Many of these complex scientific issues formed the basis of the 2007 petition filed by PANNA and NRDC and EPA therefore decided to address the Petition on a similar timeframe to EPA's expedited registration review schedule.

Although EPA expedited the chlorpyrifos registration review in an attempt to

address the novel scientific issues raised by the Petition in advance of the statutory deadline, the petitioners were dissatisfied with the pace of EPA's response efforts and have sued EPA in federal court on three separate occasions to compel a faster response to the Petition. As explained in Unit V., EPA had addressed 7 of the 10 claims asserted in the Petition by either denying the claim, issuing a preliminary denial or approving label mitigation to address the claims, but 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 it intended to propose by April 15, 2016, the revocation of all chlorpyrifos tolerances in the absence of pesticide label mitigation that ensures that exposures will be safe. 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."

On October 30, 2015, EPA issued a proposed rule to revoke all chlorpyrifos tolerances which it published in the Federal Register on November 6, 2015 (80 FR 69080). On December 10, 2015, the Ninth Circuit issued a further order requiring EPA to complete any final rule (or petition denial) and fully respond to the Petition by December 30, 2016. On June 30, 2016, EPA sought a 6-month extension to that deadline in order to allow EPA to fully consider the most recent views of the FIFRA SAP with respect to chlorpyrifos toxicology. The FIFRA SAP report was finalized and made available for EPA consideration on July 20, 2016. (Ref. 2) On August 12, 2016, the court rejected EPA's request for a 6-month extension and ordered EPA to complete its final action by

March 31, 2017 (effectively granting EPA a three-month extension). On November 17, 2016, EPA published a notice of data availability (NODA) seeking public comment on both EPA's revised risk and water assessments and reopening the comment period on the proposal to revoke all chlorpyrifos (81 FR 81049). The comment period for the NODA closed on January 17, 2017.

**V. Ruling on Petition**

This order denies the Petition on the nine remaining grounds for which EPA has not issued a final denial that can be the subject of objections under section 408(g)(2) of the FFDCA. As noted in Unit II, on July 16, 2012, EPA denied as final agency action petitioners' claim 6 that the registration of chlorpyrifos created an export hazard for workers in foreign countries. That response and the response of July 15, 2014, also included EPA's preliminary denial of petition claims 1-5 and 10 (except to the extent EPA granted that claim) and EPA's responses to those claims are now incorporated into this order as set forth below. This unit also includes EPA's basis for denying petition claims 7-9. Each specific petition claim is summarized in this Unit V. immediately prior to EPA's response to the claim.

*1. Genetic Evidence of Vulnerable Populations*

*a. Petitioners' claim*. Petitioners claim that as part of EPA's reregistration decision (which was completed in 2006 with the completion of the organophosphate cumulative risk assessment) the Agency failed to calculate an appropriate intra-species uncertainty factor (i.e., within human variability) for chlorpyrifos in both its aggregate and cumulative risk assessments (CRA). They assert that certain relevant, robust data, specifically the Furlong et al. (2006) study (Ref. 3) that addresses intra-species variability

in the behavior of the detoxifying enzyme paraoxonase (PON1), indicate that the Agency should have applied an intra-species safety factor "of at least 150X in the aggregate and cumulative assessments" rather than the 10X factor EPA applied. Petitioners conclude by noting that applying an intra-species factor of 100X or higher would require setting tolerances below the level of detection, which therefore should compel EPA to revoke all chlorpyrifos tolerances.

b. *Agency Response*. Petitioners are correct that the Agency, as part of the 2006 OP CRA, evaluated, but did not rely on Furlong et al. in setting the intra-species uncertainty factor for that assessment. The Agency did not rely on the results of the PON1 data in the OP CRA because these data do not take into consideration the complexity of OP metabolism, which involves multiple metabolic enzymes, not just PON1. In addition, EPA believes the methodology utilized in the Furlong et al. study to measure intra-species variability – i.e., combining values from multiple species (transgenic mice and human) to determine the range of sensitivity within a single species – is not consistent with well-established international risk assessment practices. Further, EPA believes that petitioners' assertion that the Furlong et al. study supports an intra-species uncertainty factor of at least 150X is based on an analysis of the data that is inconsistent with EPA policy and widely- accepted international guidance on the development of intra-species uncertainty factors. In addition, the 2008 FIFRA SAP did not support the use of the Furlong et al (2006) study alone in deriving an intra-species factor. For these reasons, and as further explained below, EPA believes it is not appropriate to solely rely on the results of the Furlong et al. study, or petitioners' interpretation of those results, for purposes of determining the intra-species uncertainty

factor. To determine that factor, EPA first uses science tools to quantitatively characterize human variability in both exposure and dosimetry, and then determines the appropriate intra-species uncertainty factor to protect sensitive populations. Specifically, for chlorpyrifos, EPA uses a physiologically-based pharmacokinetic (PBPK) model to account for human variability in the absorption, distribution, metabolism and excretion (ADME) of chemicals based on key physiological, biochemicals, and physicochemical determinants of these ADME processes, including the influence of PON1 variability.

Addressing human variability and sensitive populations is an important aspect of the Agency's risk assessment process. The Agency is well aware of the issue of PON1 and has examined the scientific evidence on this source of genetic variability. PON1 is one of the key detoxification enzymes of chlorpyrifos and is included as part of the PBPK model used by EPA in the 2014 human health risk assessment (HHRA) and 2016 revised risk assessment. Specifically, PON1 is an A-esterase which can metabolize chlorpyrifos-oxon without inactivating the enzyme. (Ref. 4) Indeed, as part of the 2008 SAP, EPA performed a literature review of PON1 and its possible use in informing the intra-species (i.e., within human variability) uncertainty factor. This literature review can be found in the draft Appendix E: Data Derived Extrapolation Factor Analysis to the draft Science Issue Paper: Chlorpyrifos Hazard and Dose Response Characterization.(Ref. 5) In sum, the Agency considered available PON1 data from more than 25 studies from diverse human populations worldwide.

The Agency focused on the PON1-192 polymorphism since it has been linked to chlorpyrifos-oxon sensitivity in experimental toxicology studies and, has been evaluated in epidemiology studies attempting to associate PON1 status with health outcomes

following OP pesticide exposure in adults and children (Holland et al., 2006; Chen et al., 2003. (Ref. 6). [Note, Holland et al (2006) and Furlong et al (2006) report findings from the same cohort. The Holland reference provides enzymes activities for specific polymorphisms in Table 4; the Furlong paper does not report such values and provides information primarily in graphical form.] However, EPA believes that focusing on PON1 variability in isolation from other metabolic action is not an appropriate approach for developing a data-driven uncertainty factor. The Agency solicited feedback from the SAP on the utility of the PON1 data, by itself, for use in risk assessment; the SAP was similarly not supportive of using such data in isolation. Specifically, the SAP report states:

> *"…the information on PON1 polymorphisms should not be used as the sole factor in a data-derived uncertainty factor for two main reasons: 1) it is only one enzyme in a complex pathway, and is subsequent to the bioactivation reaction; therefore it can only function on the amount of bioactivation product (i.e., chlorpyrifos-oxon) that is delivered to it by CYP450); and 2) the genotype of PON1 alone is insufficient to predict vulnerability because the overall level of enzyme activity is ultimately what determines detoxification potential from that pathway; thus, it is better to use PON1 status because it provides information regarding PON1 genotype and activity. Some of the data from laboratory animal studies in PON knockout animals are using an unrealistic animal model and frequently very high dose levels, and do not reflect what might happen in humans."* (Ref. 7)

Based on a detailed review of the literature and the comments from the SAP, the Agency has determined that such data are not appropriate for use alone in deriving an intra-species uncertainty factor for use in human health risk assessment. As indicated by the SAP report, multiple factors (e.g., other enzymes such as P450s, carboxylesterases, butyrylcholinesterase) are likely to impact potential population sensitivity, rendering the results of the PON1 data, by themselves, insufficiently reliable to support a regulatory

conclusion about the potential variation of human sensitivity to chlorpyrifos.

Since the 2008 SAP, several epidemiological studies have been published that considered the association between PON status/genotype and health outcome. Hofmann et al. (2009) recently reported associations between PON1 status and inhibition of butyrylcholinesterase (BuChE) in a group of pesticide handlers in Washington. The authors note that this study requires replication with larger sample size(s) and more blood samples. (Ref. 8) Given the limitations of Hofmann et al., the Agency has not drawn any conclusions from this study. The Q/R-192 and/or C/T -108 polymorphism at the promoter site have been evaluated recently as a factor affecting birth or neurobehavioral outcomes following gestational exposure to OPs. (Refs. 9, 10, 11) These studies (Eskanazi., et al., 2010 (Ref. 9); Harley et al., 2011 (Ref. 10); Engel et al., 2011 (Ref. 11)) were evaluated by EPA in preparation for the April 2012 SAP review.

Petitioners further emphasize that the Furlong et al. study supports an intra-species uncertainty factor of over 164X given the range of variability seen in that study. The 164X value is derived from sensitivity observed in transgenic mice expressing human PON1Q-192 compared with mice expressing human PON1R-192 combined with the range of plasma arylesterase (AREase) from the newborn with the lowest PON1 level compared with the mother with the highest PON1 level from a group of 130 maternal-newborn pairs from the CHAMACOS (Center for the Health Assessment of Mothers and Children of Salinas) cohort.

EPA believes it is fundamentally at odds with international risk assessment practices to combine values from both mouse and human data to determine the potential

range of variability within a single species – regardless of whether the test animals express a human PON1 enzyme. As the 2008 FIFRA SAP explained, PON1 is but a single enzyme that should not be considered in isolation to predict the overall level of enzyme activity that may affect human sensitivity to a substance. Using a 164X intra-species uncertainty factor derived from the Furlong et al. study would take this practice one step further by relying upon combined PON1 values from different species with differing overall metabolic activity to derive the intra-species factor. EPA does not believe this approach is an appropriate means of determining the potential range of intra-species variability.

Finally, petitioners' assertion that the Furlong study supports an intra-species uncertainty factor of at least 150X is based on an analysis of that study that is inconsistent with EPA policy and widely- accepted international guidance on the development of intra-species uncertainty factors. In deriving the intra-species uncertainty factor in its risk assessments, EPA is guided by the principles of the 2005 IPCS (Ref. 12) guidance on chemical specific adjustment factors (CSAFs) and the EPA's 2014 Guidance for Applying Quantitative Data to Develop Data-Derived Extrapolation Factors for Interspecies and Intraspecies Extrapolation. (Ref. 13) These guidances recommend that intra-species factors should be extrapolated from a measure of central tendency in the population to a measure in the sensitive population (i.e., to extrapolate from a typical human to a sensitive human). To base the factor on the difference between the single lowest and highest measurements in a given study, as petitioners suggest in this instance, would likely greatly exaggerate potential intra-species variability. That approach effectively assumes that the point of departure in an EPA risk assessment will be derived

from the least sensitive test subject, thereby necessitating the application of an intra-species factor that accounts for the full range of sensitivity across a species. Since EPA does not develop its PoDs in this fashion; the approach suggested by petitioners is not appropriate.

In summary, the Agency has carefully considered the issue of PON1 variability and determined that data addressing PON1 in isolation are not appropriate for use alone in deriving an intra-species uncertainty factor and that the issue is more appropriately handled using a PBPK model. Further, the derivation of the 164X value advocated by the petitioners is based on combining values from humanized mice with human measured values with a range from highest to lowest; the Furlong et al. derivation is inappropriate and inconsistent with international risk assessment practice. (Ref. 2) The 2008 FIFRA SAP did not support the PON1 data used in isolation. Finally, petitioners' statement that the Furlong et al. study supports an intra-species uncertainty factor of at least 150X likely overstates potential variability. EPA therefore denies this aspect of the Petition.

2. *Endocrine Disrupting Effects*

*a. Petitioners' claim*. Petitioners summarize a number of studies evaluating the effects of chlorpyrifos on the endocrine system, asserting that, taken together, the studies "suggest that chlorpyrifos may be an endocrine disrupting chemical, capable of interfering with multiple hormones controlling reproduction and neurodevelopment." The petitioners then assert that EPA should not have delayed consideration of endocrine effects absent finalization of the Endocrine Disruptor Screening Program (EDSP) (Ref. 14) and should have quantitatively incorporated the studies into the chlorpyrifos IRED.

*b. Agency Response.* This portion of the Petition appears largely to be a complaint

about the completeness of EPA's reregistration decision and a request that EPA undertake quantitative incorporation of endocrine endpoints into its assessment of chlorpyrifos. The Petition does not explain whether and how endocrine effects should form the basis of a decision to revoke tolerances. The basis for seeking revocation of a tolerance is a showing that the pesticide is not "safe." Petitioners have neither asserted that EPA should revoke tolerances because effects on the endocrine system render the tolerances unsafe, nor have petitioners submitted a factual analysis demonstrating that aggregate exposure to chlorpyrifos presents an unsafe risk to humans based on effects on the endocrine system. Rather, the Petition appears to collect a number of studies suggesting that chlorpyrifos may have effects on the endocrine system and that EPA should have considered those health impacts at reregistration in a quantitative assessment.

To the extent that petitioners are seeking tolerance revocation on these grounds, the Petition fails to provide a sufficient basis for revocation because, in addition to the preceding defects, the cited data do not provide quantitative data (i.e. endpoints/points of departure) that indicate endocrine effects at doses that are more sensitive than the points of departure used in the chlorpyrifos risk assessment that are based on cholinesterase inhibition. While the cited studies provide qualitative information that exposure to chlorpyrifos may be associated with effects on the androgen and thyroid hormonal pathways, these data alone do not demonstrate that current human exposures from existing tolerances are unsafe. The Agency noted similar effects during its evaluation of information submitted by People for the Ethical Treatment of Animals (PETA) and the Physicians Committee for Responsible Medicine (PCRM) during its review of existing information as part of EPA's EDSP, as discussed below. Based on the review of that

data, EPA concluded that the effects seen in those studies do not call into question EPA's prior safety determinations supporting the existing tolerances; the data do not indicate a risk warranting regulatory action, and the petitioners have provided no specific information to alter this determination.

Consequently, the Petition does not support a conclusion that existing tolerances are unsafe due to potential endocrine effects. This portion of the Petition is therefore denied.

As petitioners may be aware, since the filing of the petition, EPA has completed the evaluation of chlorpyrifos under EPA's EDSP, as required under FFDCA section 408(p) that confirms EPA's conclusions. On April 15, 2009, a **Federal Register** notice was published in which chlorpyrifos was included in the initial list of chemicals (List 1) to receive EDSP Tier 1 test orders. The EDSP program is a two-tiered screening and testing program, Tier 1 and Tier 2 tests. Tier 1 includes 11 assays in the battery; these data are intended to allow EPA to determine whether certain substances (including pesticide active and other ingredients) have the potential to interact with the endocrine system and cause an effect in humans or wildlife similar to an effect produced by a "naturally occurring estrogen, or other such endocrine effects as the Administrator may designate." The purpose of Tier 2 tests is to identify and establish a quantitative, dose-response relationship for any adverse effects that might result from the interactions with the endocrine system.

On November 5, 2009, EPA issued Tier 1 test orders to the registrants of chlorpyrifos, requiring a battery of 11 screening assays to identify the potential to interact with the estrogen, androgen, or thyroid hormonal systems. (Ref. 15)

The agency received and reviewed all 11 EDSP Tier 1 screening assays for chlorpyrifos. On June 29, 2015, the agency completed the EDSP weight of evidence (WoE) conclusions for the Tier 1 screening assays for List 1 chemicals, including chlorpyrifos. In addition to the Tier 1 data, the WoE evaluations considered other scientifically relevant information (OSRI), including general toxicity data and open literature studies of sufficient quality. In determining whether chlorpyrifos interacts with the estrogen, androgen or thyroid pathways, the agency considered the number and type of effects induced, the magnitude and pattern of responses observed across studies, taxa, and sexes. Additionally, the agency also considered the conditions under which effects occurred, in particular whether or not endocrine-related responses occurred at dose(s) that also resulted in general systemic or overt toxicity. The agency concluded that, based on weight of evidence considerations, EDSP Tier 2 testing is not recommended for chlorpyrifos since there was no evidence of potential interaction with the estrogen, androgen and thyroid pathways. The EDSP Tier 1 WoE assessment and associated data evaluation records for chlorpyrifos are available online. (Ref. 16) This assessment further supports EPA's denial of this portion of the Petition.

*3. Cancer Risks*

*a. Petitioners' claim*. Petitioners claim that the Agency "ignored" a December 2004 National Institutes of Health Agricultural Health Study (AHS) by Lee et al. (2004) (Ref. 17) that evaluated the association between chlorpyrifos and lung cancer incidence. (Ref. 17) The petition summarizes the results of the AHS study, stating that the incidence of lung cancer has a statistically significant association with chlorpyrifos exposure. The Petition then asserts that these data are highly relevant and therefore should have been

referenced in the final aggregate assessment for chlorpyrifos or the OP CRA. Petitioners do not otherwise explain whether and how these data support the revocation of tolerances or the cancellation of pesticide registrations.

*b. Agency Response.* As explained in the previous section, the basis for seeking revocation of a tolerance is a showing that the pesticide is not "safe." Claiming that EPA failed to reference certain data in its risk assessment regarding carcinogenicity does not amount to illustrating that the tolerances are unsafe. To show a lack of safety, petitioners would have to present some fact-based argument demonstrating that aggregate exposure to chlorpyrifos poses an unsafe carcinogenic risk. Petitioners have not presented such an analysis. Accordingly, EPA is denying the Petition to revoke chlorpyrifos tolerances or cancel chlorpyrifos registrations to the extent the Petition relies on claims pertaining to carcinogenicity.

Despite the inadequacy of petitioners' cancer claims, in the course of the Agency's review of chlorpyrifos, EPA has examined the Lee et al. study cited by petitioners (Ref. 17) among other lines of evidence. EPA has concluded that the Lee et al. investigation does not alter the Agency's weight of evidence determination concerning chlorpyrifos' carcinogenic potential, and therefore does not alter the Agency's current cancer classification for chlorpyrifos. Specifically, the Agency does not believe this evidence raises sufficient grounds for concern regarding chlorpyrifos that EPA should consider initiating action based upon this information that might lead to revocation of the chlorpyrifos tolerances or cancellation of the chlorpyrifos registrations.

The Agency was aware of the December 2004 study cited by petitioners. While Lee et al. observed a possible association between chlorpyrifos use and the incidence of

lung cancer, the authors also stressed that further evaluation was necessary before concluding the association was causal in nature.(Ref. 17) Additional evaluation is necessary because of possible alternative explanations for the Lee et al. study, which include unmeasured confounding factors or confounding factors not fully accounted for in the analysis, and possible false positive results due to the performance of multiple statistical tests.

EPA has been a collaborating agency with the AHS since 1993, and continues to closely monitor the AHS literature. The Agency is working closely with the AHS researchers to clearly understand the results of their research efforts to ensure the Agency appropriately interprets these data as future studies are published. Between 2003 and 2009 there have been six nested case-control analyses within the AHS which evaluated the use of a number of agricultural pesticides, including chlorpyrifos, in association with specific anatomical cancer sites, in addition to the previously published cohort study (Ref. 17) cited by the petitioners. As noted below, both the Agency and Health Canada have comprehensively reviewed these data.

In accordance with the Agency's 2005 Guideline for Cancer Risk Assessment (Ref. 18), chlorpyrifos is classified as "Not Likely to be Carcinogenic to Humans" based on the lack of evidence of carcinogenicity in male or female mice and male or female rats. In chronic toxicity/ carcinogenicity studies, animals received chlorpyrifos in their feed every day of their lives (78 weeks for mice and 104 weeks for rats) at doses thousands of times greater than any anticipated exposure to humans from authorized uses. There was no evidence of cancer in the experimental animal studies. Additionally, available evidence from *in vivo* and *in vitro* assays did not support a mutagenic or

genotoxic potential of chlorpyrifos.

Recently, the Agency conducted its own review of the six nested case-control analyses and one cohort study within the AHS concerning the carcinogenic potential of chlorpyrifos. (Ref. 19) EPA concluded with respect to the AHS lung cancer results that the findings are useful for generating hypotheses, but require confirmation in future studies. This conclusion is consistent with that of researchers from Health Canada. Specifically, Weichenthal et al. (2010) (Ref. 20) published a review article in Environmental Health Perspectives on pesticide exposure and cancer incidence in the AHS cohort. Their review of these same studies concluded that the weight of experimental toxicological evidence does not suggest that chlorpyrifos is carcinogenic, and that epidemiologic results currently available from the AHS are inconsistent, lack replication, and lack a coherent biologically plausible carcinogenic mode of action. The authors did note positive exposure-response associations for chlorpyrifos and lung cancer in two separate evaluations.

In summary, while there is initial suggestive epidemiological evidence of an association between chlorpyrifos and lung cancer to only form a hypothesis as to a carcinogenic mode of action, additional research (including follow-up AHS research) is needed to test the hypothesis. Consequently, at this time it is reasonable to conclude chlorpyrifos is not a carcinogen in view of the lack of carcinogenicity in the rodent bioassays and the lack of a genotoxic or mutagenic potential. The Agency concludes that existing epidemiological data (including Lee et al.) do not change the current weight of the evidence conclusions. The Agency continues to believe there is not a sufficient basis to alter its assessment of chlorpyrifos as not likely to be carcinogenic to humans when

multiple lines of evidence are considered (e.g., epidemiology findings, rodent bioassay, genotoxicity); therefore, chlorpyrifos cancer risk would not be a factor in any potential Agency risk determination to revoke tolerances for chlorpyrifos.

*4. CRA misrepresents risks, failed to apply FQPA10X Safety Factor*

*a. Petitioners' claim.* Petitioners assert that EPA relied on limited data and inaccurate interpretations of data to support its decision to remove the FQPA safety factor in the 2006 OP CRA. Specifically, the petitioners challenge the Agency's use of data from a paper by Zheng et al. (2000) (Ref. 21) claiming that, in contrast to the Agency's analysis of the study data, the data does show an obvious difference between juvenile and adult responses to chlorpyrifos. Petitioners conclude by asserting that the Zheng et al. study supports using a 10X safety factor for chlorpyrifos in the CRA.

*b. Agency Response.* Petitioners' assertions do not provide a sufficient basis for revoking chlorpyrifos tolerances. As explained previously, the ground for seeking revocation of a tolerance is a showing that the pesticide is not "safe." The petitioners' claim that the data EPA relied upon support a different FQPA safety factor for chlorpyrifos in the CRA does not amount to a showing that chlorpyrifos tolerances are unsafe. To show a lack of safety, petitioners would have to present a factual analysis demonstrating that the lack of a 10X safety factor in the CRA for chlorpyrifos poses unsafe cumulative exposures to the OPs. Petitioners have not made such a showing. For this reason, EPA is denying the petitioners' request to revoke chlorpyrifos tolerances or cancel chlorpyrifos registrations to the extent that request relies on claims pertaining to EPA's failure to provide a 10X safety factor in the 2006 CRA based on the results of the Zheng et al. study.

Despite the inadequacy of petitioners' FQPA safety factor claims, EPA examined the evidence cited by petitioners for the purpose of evaluating whether the evidence raises sufficient grounds for concern regarding chlorpyrifos that EPA should consider initiating the actions sought by the petitioners.

In general, when the Agency conducts a cumulative assessment, the scope of cumulative risk is limited to the common mechanism endpoint -- which in this case of the 2006 OP CRA, was cholinesterase inhibition, the primary toxicity mode of action for the OPs. As such, for the OP CRA, experimental toxicology data on AChE inhibition were used for developing relative potency estimates, points of departure, and informing the FQPA safety factor used in the OP CRA. EPA relied on brain AChE data from adult female rats dosed for 21 days or longer for estimating relative potency and points of departure. At approximately three weeks of oral exposure to OPs, AChE inhibition reaches steady state in the adult rat such that continued dosing does not result in increased inhibition. This timeframe of toxicity (21-days and longer) was selected as there was high confidence in the potency estimates derived from the steady state toxicology studies due to the stability of the AChE inhibition.

The Agency's 2006 OP CRA contained EPA's complete FQPA safety factor analysis, (Ref. 22) which involved consideration of pre-natal and post-natal experimental toxicology studies, in addition to exposure information. In the OP CRA, pre-natal exposure AChE studies in rats show that the fetus is no more sensitive than the dam to AChE inhibition and the fetus is often less sensitive than the dam. Thus, evaluating the potential for increased toxicity of juveniles from post-natal exposure was a key

component in determining the magnitude of the FQPA safety factors in the OP CRA. Furthermore, because characteristics of children are directly accounted for in the cumulative exposure assessment, the Agency's methods did not underestimate exposure to OPs.

In the 2006 OP CRA, each OP was assigned a 10X FQPA safety factor unless chemical-specific AChE data on young animals were available to generate a data derived safety factor. To best match the relative potency factor (RPF)s and PODs based on repeated dosing, the Agency used repeated dosing data in juveniles for developing the FQPA safety factors. For chlorpyrifos, at the time of the 2006 OP CRA, the only such data available were from the Zheng et al. literature study.

The petitioners are correct that Dr. Carey Pope of Oklahoma State University provided the Agency with the raw data from the Zheng et al. study. These raw data were used to develop the plot in the 2006 OP CRA which was reproduced in the Petition. Petitioners accurately note that for other OPs a benchmark dose modeling approach was used and that no BMD values were reported for chlorpyrifos. In determining the FQPA safety factor, petitioners claim that the Agency misinterpreted the brain AChE data from Zheng et al.

As shown in the plot reproduced on page 15 of the Petition, the dose-response data in the Zheng et al. study are variable and lack a monotonic shape at the low dose end of the dose response curve. The Agency acknowledges that at the high dose, the pups appear to be more sensitive. However, at the low dose end of the response curve, relevant for human exposures and, thus, the cumulative risk assessment (i.e., at or near the 10% inhibition level), little to no difference is observed. Therefore, despite the lack

of BMD estimates for the Zheng et al. study, the Agency is confident in the value used to address the common mechanism endpoint (AChE inhibition) addressed in the 2006 CRA. Since that time, the Agency attempted BMD modeling of the Zheng et al. data as part of the 2011 preliminary chlorpyrifos HHRA (Ref. 23) which yielded low confidence results due to the variability in the data.

Dow AgroSciences submitted a comparative cholinesterase study (CCA) for chlorpyrifos. CCA studies are specially designed studies to compare the dose-response relationship in juvenile and adult rats. This CCA study includes two components: 1) acute, single dosing in post-natal day 11 and young adult rats and 2) 11-days of repeating dosing in rat pups from PND11-21 and 11-days of repeated dosing in adult rats. The CCA study for chlorpyrifos is considered by EPA to be high quality and well-designed. The preliminary risk assessment for chlorpyrifos' reports BMD estimates from this CCA study. Specifically, for the repeated dosing portion of the study, the $BMD_{10s}$ of 0.80 (0.69 $BMDL_{10}$) and 1.0 (0.95 $BMDL_{10}$) mg/kg/day respectively for female pups and adults support the FQPA safety factor of 1X for the AChE inhibition endpoint used in the 2006 OP CRA. As such, petitioners' claims regarding the CRA and FQPA safety factor is denied.

*5. Over-reliance on registrant data.*

*a. Petitioners' claims.* Petitioners assert that in reregistering chlorpyrifos EPA "cherry picked" data, "ignoring robust, peer-reviewed data in favor of weak, industry-sponsored data to determine that chlorpyrifos could be re-registered and food tolerances be retained." As such, the Agency's reassessment decision is not scientifically defensible.

*b. Agency response.* This portion of the Petition does not purport to be an independent basis for revoking chlorpyrifos tolerances or cancelling chlorpyrifos registrations. Rather, this claim appears to underlie petitioners' arguments in other sections of the Petition. While petitioners claim that EPA ignored robust, peer-reviewed data in favor of weak, industry-sponsored data for the reregistration of chlorpyrifos, petitioners do not cite to any studies other than those used to support their other claims. In general, petitioners did not provide any studies in the Petition that EPA failed to evaluate. Since the specific studies cited by petitioners are not associated with this claim, but rather their other claims, EPA's response to the specific studies are, therefore, addressed in its responses to petitioners' other claims. However, EPA explains below why, as a general matter, the Agency does not believe it "over-relied" on registrant data in evaluating the risks of chlorpyrifos in its 2006 reregistration decision.

In spite of petitioners' claim, the Agency does not ignore robust, peer-reviewed data in favor of industry-sponsored data. Further, EPA has a very public and well-documented set of procedures that it applies to the use and significance accorded all data utilized to inform risk management decisions. Registrant generated data, in response to FIFRA and FFDCA requirements, are conducted and evaluated in accordance with a series of internationally harmonized and scientifically peer-reviewed study protocols designed to maintain a high standard of scientific quality and reproducibility. (Refs. 23 and 24).

Additionally, to further inform the Agency's risk assessment, EPA is committed to the consideration of other sources of information such as data identified in the open, peer-reviewed literature and information submitted by the public as part of the regulatory

evaluation of a pesticide. An important issue, when evaluating any study, is its scientific soundness and quality, and thus, the level of confidence in the study findings to contribute to the risk assessment.

The literature was searched, fully considered, and provided additional information on, chlorpyrifos mode of action, pharmacokinetics, epidemiology, neurobehavioral effects in laboratory animals, and age dependent sensitivity to cholinesterase inhibition.

Therefore, by evaluating registrant data in accordance with internationally harmonized and scientifically peer-reviewed study protocols, undertaking thorough open literature searches, and considering information provided by the public, the Agency is confident that its assessment for chlorpyrifos in 2006 was reasonably based upon the best available science at the time of the assessment. Previous sections of this response to petitioners' claims regarding the Agency's inadequate use of various data only further highlights and supports the scientifically defensible results of the Agency's assessment. Petitioners' claim that the Agency overly relies on registrant data is therefore denied.

*6. EPA has failed to properly address the exporting hazard in foreign countries from chlorpyrifos.*

As noted in Unit II., in EPA's July 16, 2012 interim petition response EPA issued a final denial of this claim. That denial constituted final agency action and EPA is not reopening consideration of that claim.

*7.-9. EPA failed to quantitatively incorporate data demonstrating long-lasting effects from early life exposure to chlorpyrifos in children; EPA disregarded data demonstrating that there is no evidence of a safe level of exposure during pre-birth and early life stages; EPA failed to cite or quantitatively incorporate studies and clinical*

*reports suggesting potential adverse effects below 10% cholinesterase inhibition.*

a. *Petitioners' claims.* The petitioners assert that human epidemiology and rodent developmental neurotoxicity data suggest that pre-natal and early life exposure to chlorpyrifos can result in long-lasting, possibly permanent damage to the nervous system and that these effects are likely occurring at exposure levels below 10% cholinesterase inhibition, EPA's existing regulatory standard for chlorpyrifos and other OPs. They assert that EPA has therefore used the wrong endpoint as a basis for regulation and that, taking into account the full spectrum of toxicity, chlorpyrifos does not meet the FFDCA safety standard or the FIFRA standard for registration.

*b. Agency response.* EPA has grouped claims 7-9 together because they fundamentally all raise the same issue: whether the potential exists for chlorpyrifos to cause neurodevelopmental effects in infants and children from exposures (either to mothers during pregnancy or directly to infants and children) that are lower than those resulting in 10% cholinesterase inhibition – the basis for EPA's long-standing point of departure in regulating chlorpyrifos and other OPs. While petitioners may perhaps disagree, unlike the claims addressed above, these claims were not truly challenges to EPA's 2006 reregistration decision for chlorpyrifos, but rather, challenges to EPA's ongoing approval of chlorpyrifos under FIFRA and the FFDCA that rely in large measure on data published after EPA completed both its 2001 chlorpyrifos Interim Reregistration Decision and the 2006 OP CRA that concluded the reregistration process for chlorpyrifos and all other OPs. As matters that largely came to light after the completion of reregistration, these petition issues are issues to be addressed as part of the registration review of chlorpyrifos – the next round of re-evaluation under section 3(g) of FIFRA. As

petitioners are aware, past EPA administrations prioritized the registration review of the OPs in no small measure to begin to focus on the question of OP neurodevelopmental toxicity, which was, and remains, an issue at the cutting edge of science, involving significant uncertainties. EPA has three times presented approaches and proposals to the FIFRA SAP for evaluating recent epidemiologic data (some of which is cited in the Petition) exploring the possible connection between *in utero* and early childhood exposure to chlorpyrifos and adverse neurodevelopmental effects. The SAP's reports have rendered numerous recommendations for additional study and sometimes conflicting advice for how EPA should consider (or not consider) the epidemiology data in conducting EPA's registration review human health risk assessment for chlorpyrifos. While industry and public interest groups on both sides of this issue can debate what the recommendations mean and which recommendations should be followed, one thing should be clear to all persons following this issue: the science on this question is not resolved and would likely benefit from additional inquiry.

EPA has, however, been unable to persuade the 9th Circuit Court of Appeals that further inquiry into this area of unsettled science should delay EPA's response to the Petition. Faced with an order requiring EPA to respond to the Petition, in October 2015, EPA chose to issue a proposed rule to revoke all chlorpyrifos tolerances based in part on the uncertain science surrounding neurodevelopmental toxicity suggested by certain epidemiology studies. The comments EPA has received on that proposal and on EPA's November 17, 2016 NODA suggest that there continue to be considerable areas of uncertainty with regard to what the epidemiology data show and deep disagreement over how those data should be considered in EPA's risk assessment.

Although not a legal consideration, it is important to recognize that for many decades chlorpyrifos has been and remains one of the most widely used pesticides in the United States, making any decision to retain or remove this pesticide from the market an extremely significant policy choice. In light of the significance of this decision and in light of the significant uncertainty that exists regarding the potential for chlorpyrifos to cause adverse neurodevelopmental effects, EPA's preference is to fully explore approaches raised by the SAP and commenters on the proposed rule, and possibly seek additional authoritative peer review of EPA's risk assessment prior to finalizing any regulatory action in the course of registration review. As the 9th Circuit has made clear in its August 12, 2016 order in *PANNA v. EPA*, EPA must provide a final response to the Petition by March 31, 2017, regardless of whether the science remains unsettled and irrespective of whatever options may exist for more a complete resolution of these issues during the registration review process.

While EPA acknowledges its obligation to respond to the Petition as required by the court, the court's order does not and cannot compel EPA to complete the registration review of chlorpyrifos in advance of the October 1, 2022 deadline provided in section 3(g) of FIFRA, 7 U.S.C. 136a(g). Although past EPA administrations had chosen to attempt to complete that review several years in advance of the statutory deadline (and respond to the Petition on the same time frame), it has turned out that it is not possible to fully address these issues early in the registration review period. As a result, EPA has concluded that it should alter its priorities and adjust the schedule for chlorpyrifos so that it can complete its review of the science addressing neurodevelopmental effects prior to making a final registration review decision whether to retain, limit or remove

chlorpyrifos from the market. Accordingly, EPA is denying these Petition claims and intends to complete a full and appropriate review of the neurodevelopmental data before either finalizing the proposed rule of October 30, 2015, or taking an alternative regulatory path.

EPA's denial of the Petition on the grounds provided above is wholly consistent with governing law. The petition provision in FFDCA section 408(d) does not address the timing for responding to this petition nor does it limit the extent to which EPA may coordinate its petition responses with the registration review provisions of FIFRA section 3(g). Further, provided EPA completes registration review by October 1, 2022, Congress otherwise gave the EPA Administrator the discretion to determine the schedule and timing for completing the review of the approximately over 1000 pesticide active ingredients currently subject to evaluation under section 3(g). EPA may lawfully re-prioritize the registration review schedule developed by earlier administrations provided that decision is consistent with law and an appropriate exercise of discretion. *See Federal Communications Commission v. Fox Television Stations*, 129 S.Ct. 1800 (2009) (Administrative Procedure Act does not require that a policy change be justified by reasons more substantial than those required to adopt a policy in the first instance). Nothing in FIFRA section 3(g) precludes EPA from altering a previously established registration review schedule. Given the absence of a clear statutory directive, FIFRA and the FFDCA provide EPA with discretion to take into account EPA's registration review of a pesticide in determining how and when the Agency responds to FFDCA petitions to revoke tolerances. As outlined above, given the importance of this matter and the fact that critical questions remain regarding the significance of the data

addressing neurodevelopmental effects, EPA believes there is good reason to extend the registration review of chlorpyrifos and therefore to deny the Petition. To find otherwise would effectively give petitioners under the FFDCA the authority to re-order scheduling decisions regarding the FIFRA registration review process that Congress has vested in the Administrator.

*10. Inhalation Exposure from Volatilization*

*a. Petitioners' claim.* Petitioners assert that when EPA completed its 2006 OP CRA, EPA failed to consider and incorporate significant exposures to chlorpyrifos-contaminated air that exist for some populations in communities where chlorpyrifos is applied. Petitioners assert that these exposures exceeded safe levels when considering cholinesterase inhibition as a point of departure and that developmental neurotoxicity may occur at even lower exposure levels than those resulting in cholinesterase inhibition.

*b. Agency response.* To the extent petitioners are asserting that human exposure to chlorpyrifos spray drift and volatilized chlorpyrifos present neurodevelopmental risks for infants and children, EPA is denying this claim for the reasons stated above in our response to claims 7-9. As noted, EPA believes that, given the uncertainties associated with this identified risk concern, the appropriate course of action is for EPA to deny the Petition and work to further resolve this area of unsettled science in the time remaining for the completion of registration review under section 3(g) of FIFRA.

With respect to petitioners' claim that exposures to spray drift and volatilized chlorpyrifos present a risk from cholinesterase inhibition, EPA is denying the Petition for the reasons previously identified in EPA's Spray Drift Mitigation Decision of July 16, 2012 [EPA-HQ-OPP-2008-0850] and EPA's interim response of July 15, 2014 [EPA-

HQ-OPP-2007-1005] addressing chlorpyrifos volatilization. In the Spray Drift Mitigation Decision, EPA determined that the chlorpyrifos registrants' adoption of label mitigation (in the form of label use rate reductions and no spray buffer zones) eliminated risk from cholinesterase inhibition as a result of spray drift. As for risks presented by volatilized chlorpyrifos that may occur following application, EPA's July 15, 2014 interim response to the Petition explained that recent vapor phase inhalation studies for both chlorpyrifos and chlorpyrifos-oxon made clear that neither vapor phase chlorpyrifos nor chlorpyrifos-oxon presents a risk of cholinesterase inhibition. Specifically, those studies, as indicated in EPA's memorandum, *Chlorpyrifos: Reevaluation of the Potential Risks from Volatilization in Consideration of Chlorpyrifos Parent and Oxon Vapor Inhalation Toxicity Studies* (Ref. 25), revealed that levels of chlorpyrifos and chlorpyrifos-oxon in vapor form are much lower than the levels seen in earlier aerosol studies that are better suited for evaluating spray drift. Indeed, no cholinesterase inhibition was observed in either volatility study. What is clear from these data is that the air cannot hold levels of volatilized chlorpyrifos or its oxon that are capable of causing adverse effects from cholinesterase inhibition.

**VI. Regulatory Assessment Requirements**

As indicated previously, this action announces the Agency's order denying a petition filed, in part, under section 408(d) of FFDCA. As such, this action is an adjudication and not a rule. The regulatory assessment requirements applicable to rulemaking do not, therefore, apply to this action.

**VII. Submission to Congress and the Comptroller General**

The Congressional Review Act, 5 U.S.C. 801 *et seq*., does not apply because this

action is not a rule for purposes of 5 U.S.C. 804(3).

**IX. References**

The following is a listing of the documents that are specifically referenced in this document. The docket includes these documents and other information considered by EPA, including documents that are referenced within the documents that are included in the docket, even if the referenced document is not physically located in the docket. For assistance in locating these other documents, please consult the technical person listed under FOR FURTHER INFORMATION CONTACT.

1. 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 *http://www.regulations.gov*.

2. FIFRA Scientific Advisory Panel (2016). "Chlorpyrifos: Analysis of Biomonitoring Data". Available at: *https://www.epa.gov/sap/meeting-materials-april-19-21-2016-scientific-advisory-panel*.

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9. Hofmann, J.N., Keifer, M.C., Furlong, C.E., De Roos, A.J., Farin., F.M., Fenske, R.A., van Belle, G., Checkoway, H. (2009) Serum Cholinesterase Inhibition in Relation to Paraoxonase-1 (PON1) Status among Organophosphate-Exposed Agricultural Pesticide Handlers./ Environ Health Perspect 117:1402–1408 (2009). doi:10.1289/ehp.0900682. Available at http://dx.doi.org/ [Online 9 June 2009].

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Study Exposed to Organophosphate Pesticides in Utero. Environmental Health Perspectives. Vol 118 (12): 1775-1781).

11. Harley KG, Huen K, Schall RA, Holland NT, Bradman A, et al. (2011) Association of Organophosphate Pesticide Exposure and Paraoxonase with Birth Outcome in Mexican-American Women. PLoS ONE 6(8): e23923. doi:10.1371/journal.pone.0023923.

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**Authority:** 7 U.S.C. 136 *et seq.* and 21 U.S.C. 346a.

Dated: March 29, 2017.

E. Scott Pruitt,

Administrator.

[FR Doc. 2017-06777 Filed: 4/4/2017 8:45 am; Publication Date: 4/5/2017]

# ATTACHMENT 2

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

OFFICE OF CHEMICAL SAFETY AND
POLLUTION PREVENTION

**MEMORANDUM**

**Date: November 3, 2016**

**SUBJECT: Chlorpyrifos**: Revised Human Health Risk Assessment for Registration Review

**PC Code:** 059101
**Decision No.:** 522687
**Petition No.:** NA
**Risk Assessment Type:** Single Chemical Aggregate
**TXR No.:** NA
**MRID No.:** NA

**DP Barcode:** D436317
**Registration No.:** NA
**Regulatory Action:** Registration Review
**Case No.:** NA
**CAS No.:** 2921-88-2
**40 CFR:** 40 CFR§180.342

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**THROUGH:** Michael Metzger, Branch Chief
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And

Dana Vogel, Division Director
Health Effects Division (7509P)

**TO:** Dana Friedman, Chemical Review Manager
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## 1.0 Executive Summary

This document presents the revised human health risk assessment for the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) Registration Review of the organophosphate (OP) insecticide chlorpyrifos.

*Background*
A preliminary human health risk assessment (HHRA) for chlorpyrifos was completed on June 30, 2011 (D. Drew *et. al*, D388070, 06/30/2011) as part of the FIFRA Section 3(g) Registration Review program. A revised HHRA was completed in 2014 (D. Drew *et. al*, D424485, 12/29/2014) to address comments received on the preliminary HHRA and to incorporate new information and new approaches that had become available since the June 2011 risk assessment. Most notably, the 2014 revised HHRA incorporated the following: (1) a physiologically-based pharmacokinetic-pharmacodynamic (PBPK-PD) model for deriving toxicological points of departure (PoDs) based on 10% red blood cell (RBC) acetyl cholinesterase (AChE) inhibition; and (2) evidence on neurodevelopmental effects in fetuses and children resulting from chlorpyrifos exposure as reported in epidemiological studies, particularly the results from the Columbia Center for Children's Environmental Health (CCCEH) study on pregnant women which reported an association between fetal cord blood levels of chlorpyrifos and neurodevelopmental outcomes. The 2014 revised HHRA retained the 10X Food Quality Protection Act (FQPA) Safety Factor (SF) because of the uncertainties that neurodevelopmental effects may be occurring at doses lower than those that cause 10% RBC AChE inhibition and used for the PoD.

Based on the aggregate risks identified in 2014 (D. Drew *et. al*, D424485, 12/29/2014), a proposed rule (PR) for revoking all tolerances of chlorpyrifos was published in the Federal Register on November 6, 2015 (80 FR 69079). At that time, the EPA had not completed a refined drinking water assessment or additional analysis of the hazard from chlorpyrifos that was suggested by several commenters to the EPA's 2014 registration review revised HHRA. Those commenters raised the concern that the use of 10% RBC AChE inhibition for deriving PoDs for chlorpyrifos may not provide a sufficiently health protective human health risk assessment given the potential for neurodevelopmental outcomes. Accordingly, following the issuance of the proposed rule, the EPA conducted additional hazard analyses using data on chlorpyrifos levels in fetal cord blood (reported by the CCCEH study investigators) as the source for new PoDs for risk assessment.

The EPA consulted the FIFRA Scientific Advisory Panel (SAP) for scientific advice on the proposed approach of using the CCCEH cord blood data at a meeting on April 19 – 21, 2016. The 2016 SAP did not support using the cord blood data quantitatively for deriving PoDs. However, the Panel concluded that epidemiology and toxicology studies suggest there is evidence for adverse health outcomes associated with chlorpyrifos exposures below levels that result in 10% RBC AChE inhibition, which was used as the PoD in the EPA's 2014 RHHRA and for the 2015 proposed revocation rule. The SAP therefore appears to have rejected both the approach the EPA put forward in its proposed rule derived from the 2014 risk assessment as well as the EPA's initial efforts to address the results of the CCCEH study quantitatively.

The SAP report, however, did present the EPA with a path forward for a third approach to setting the PoDs. First, as a foundation, it is important to note that the SAP was supportive of the EPA's use of the PBPK model as a tool for assessing internal dosimetry from typical Office of Pesticide Programs (OPP) exposure scenarios using peer reviewed exposure assessment approaches (e.g., food, water, residential, occupational). Use of the PBPK model coupled with typical exposure scenarios provides the strongest scientific foundation for chlorpyrifos human health risk assessment and is the approach used in this 2016 assessment. Given that the window(s) of susceptibility are currently not known for the observed neurodevelopmental effects, and the uncertainties associated with quantitatively interpreting the CCCEH cord blood data, the SAP recommended that the agency use a time weighted average (TWA) blood concentration of chlorpyrifos for the CCCEH study cohort as the PoD for risk assessment. The EPA has chosen to follow that advice in this assessment. Thus, for this assessment, the PBPK model was used to determine the TWA blood level expected from post-application exposures from the chlorpyrifos indoor crack and crevice use scenario. This scenario was selected as it represents the most appropriate exposure for the women in the CCCEH cohort (i.e., crack and crevice was the predominant application type during the time of the CCCEH study and is considered protective of other possible exposures for the women in the cohort). In order to derive a TWA of chlorpyrifos concentrations in blood for a predicted risk assessment endpoint, the dose reconstruction analysis assumed exposures for 2 hours per day with a daily shower, for a total of 30 days. Additionally, chlorpyrifos residues were assumed to dissipate 10% daily; that is, the total amount of residue available for transfer from the treated floor is assumed to reduce by 10% for each subsequent day of exposure until the end of the 30$^{th}$ day prior to the next application.

The TWA blood level was used as the internal dose for determining separate PoDs for infants, children, and adults exposed to chlorpyrifos. These separate PoDs have been calculated by PBPK modeling for dietary (food, drinking water), residential, and occupational exposures. With the exception of the acute (single day) exposure assessment for non-occupational bystander post-application inhalation exposures, only steady state[1] (repeat) exposure durations are considered in this assessment as assessing the steady state exposure duration most closely matches the TWAs calculated for the PoDs. The PoDs derived from the TWA blood level are protective of any additional acute exposures to chlorpyrifos.

The TWA blood level resulting from chlorpyrifos exposure from the crack and crevice scenario is considered a lowest-observed-adverse-effect-level (LOAEL) rather than a no-observed-adverse-effect-level (NOAEL), since this is the exposure level likely to be associated with neurodevelopmental effects reported in the CCCEH study. In situations where the agency selects a PoD from a study where a NOAEL has not been identified, the EPA generally will retain the FQPA SF of 10X to account for the uncertainty in using a LOAEL. Therefore, the 10X FQPA SF has been retained in this revised risk assessment for chlorpyrifos. The revised risk assessment also applies a 10X uncertainty factor for intraspecies variability because of the lack

[1] Organophosphates (OPs), including chlorpyrifos, exhibit a phenomenon known as steady state AChE inhibition. After repeated dosing at the same level, the degree of inhibition comes into equilibrium with the production of new, uninhibited enzyme. At this point, the amount of AChEI at a given dose remains relatively consistent across duration. In general, OPs reach steady state within 2-3 weeks. Therefore, for OPs it is appropriate to assess steady state exposure durations (up to 21 days) instead of longer term exposures. The steady state point of departure is protective of any longer exposure duration, including chronic exposure.

of sufficient information to reduce or remove this factor. Typically, the agency uses animal studies for selection of PoDs and, as such, retains a 10X interspecies factor for extrapolation of the animal data to assess human health. However, with use of the PBPK-PD model which accounts for the pharmacokinetic and pharmacodynamic differences between animals and humans to derive PoDs, it is appropriate to reduce the interspecies factor to 1X. Therefore, the total uncertainty factor for chlorpyrifos in this 2016 risk assessment is 100X.

For the dietary assessment, PoDs are divided by the total uncertainty factor (100) to derive a population adjusted dose (PAD). The chlorpyrifos exposure values resulting from dietary modeling are compared to the PAD. There are potential risks of concern when estimated dietary risk exceeds 100% of the PAD.

For the residential and occupational assessments, margins of exposure (MOEs) are calculated by comparing the PoDs to the calculated exposures for each scenario. The resulting MOEs are then compared to the level of concern (LOC) of 100 (the total uncertainty factor is the LOC). If calculated MOEs are less than 100 then a risk of concern is identified for that exposure scenario.

This 2016 human health risk assessment only provides limited summary information and substantially relies on the following previous documents developed for chlorpyrifos, and the updated drink water assessment, which contain more detailed evaluations of the risk assessment approach, scientific literature, and the PBPK model:

- D. Drew *et al.,* Chlorpyrifos: Revised Human Health Risk Assessment for Registration Review, December 29, 2014, D424485;
- U.S. Environmental Protection Agency, Literature Review on Neurodevelopment Effects & FQPA Safety Factor Determination for the Organophosphate Pesticides, September 15, 2015, D331251;
- R. Bohaty and J. Hetrick. Chlorpyrifos Registration Review Drinking Water Assessment, April 14, 2016, D432921
- U.S. Environmental Protection Agency, Chlorpyrifos Issue Paper: Evaluation of Biomonitoring Data from Epidemiology Studies, March 11, 2016 and supporting analyses presented to the FIFRA Scientific Advisory Panel's (SAP) meeting on April 19-21, 2016, (EPA-HQ-OPP-2016-0062).

*Use Profile*

Chlorpyrifos is a broad-spectrum, chlorinated OP insecticide. Registered use sites include a large variety of food crops, and non-food use settings. Public health uses include aerial and ground-based fogger adulticide treatments to control mosquitoes. There is a wide range of registered formulations, application rates, and application methods. Registered labels generally require that handlers use normal work clothing (i.e., long sleeved shirt and pants, shoes and socks) and coveralls, chemical resistant gloves, and dust/mist respirators. Also, some products are marketed in engineering controls such as water soluble packets. The restricted entry intervals (REIs) on the registered chlorpyrifos labels range from 24 hours to 5 days. The pre-harvest intervals (PHIs) range from 0 days (Christmas trees) to 365 days (ginseng).

*Dietary Risk Assessment*

This assessment indicates that steady state dietary exposure analysis is highly refined. The large

majority of food residues used were based upon U. S. Department of Agriculture's Pesticide Data Program (PDP) monitoring data. Percent crop treated information and food processing factors were included, where available. All commodities with U.S. tolerances for residues of chlorpyrifos are included in the assessment.

The steady state dietary (food only) exposures for chlorpyrifos are of risk concern (> 100% steady state PAD for food ($ssPAD_{food}$)) at the 99.9$^{th}$ percentile of exposure for all population subgroups analyzed. Children (1-2 years old) is the population subgroup with the highest risk estimate at 14,000% of the $ssPAD_{food}$.

For chlorpyrifos, a drinking water level of comparison (DWLOC) approach is used to calculate the amount of exposure available in the dietary 'risk cup' for chlorpyrifos in drinking water after accounting for chloropyrifos exposure from food. This DWLOC is then compared to the estimated drinking water concentration (EDWC) to determine if there is a risk of concern for drinking water exposures. However, because this assessment indicates that dietary risks from food alone are of concern it is not possible to calculate a DWLOC; essentially the steady state DWLOC is '0' after accounting for food exposures.

Hypothetically, if there were no exposure to chlorpyrifos from food and the entire dietary 'risk cup' was available for drinking water, the resulting steady state DWLOC for infants (the most highly exposed population subgroup for water) would be 0.014 ppb. An EDWC at or exceeding this concentration would be considered a risk of concern for exposures to chlorpyrifos in drinking water. The refined chlorpyrifos EDWCs are presented in the revised drinking water assessment (DWA) (Bohaty, R., 4/14/2016, D432921, Chlorpyrifos Revised Drinking Water Assessment for Registration Review).

*Residential (Non-occupational) Risk Assessment*
Residential post-application exposures can occur for adults and children golfing on chlorpyrifos-treated courses. The residential post-application assessment considered and incorporated all relevant populations and chemical-specific turf transferable residue (TTR) data. This assessment indicates that all residential post-application exposures are of concern (i.e., MOEs are < 100) on the day of application (Day 0); all MOEs < 1 (LOC = 100). Further, all residential post-application exposure scenarios assessed following aerial and ground Ultra Low Volume (ULV) mosquitocide applications result in risks of concern; MOEs ranged from < 1 to 68 (LOC = 100).

*Non-Occupational Spray Drift Exposure and Risk Assessment*
A quantitative non-occupational spray drift (from treatment of agricultural fields) assessment was conducted for this assessment. Adult dermal and children's (1 < 2 year old) dermal and incidental oral risk estimates from indirect exposure to chlorpyrifos from spray drift result in risk estimates of concern at the field edge. All scenarios require buffer distances of > 300 feet to be below the level of concern.

*Non-Occupational Bystander Post-Application Inhalation Exposure and Risk Assessment*
In the 2014 risk assessment, the agency did not include a quantitative assessment of post-application inhalation exposure to bystanders. This assessment was not included since two vapor-phase AChE inhibition inhalation toxicity studies were submitted and reviewed which

demonstrated that no inhibition of AChE occurred even at the saturation concentration. Therefore, it was assumed that there were no anticipated risks of concern from exposure to the volatilization of either chlorpyrifos or chlorpyrifos oxon. However, in the current assessment, the points of departure for risk assessment have been chosen to be protective of potential neurological effects that occur below levels where AChE inhibition could occur. For that reason, a quantitative bystander/volatilization assessment has been included in this update.

The EPA has assessed residential bystander exposure from field volatilization of applied chlorpyrifos based on available *ambient* (five studies/11 locations) and *application site* (one study/2 locations) air monitoring data. Of the 11 acute *ambient* air concentrations assessed, six resulted in risk estimates that are of concern (i.e., MOEs < 100). Only one steady-state *ambient* air concentration resulted in a risk estimate not of concern (i.e., MOEs > 100). For the *application site* air concentrations assessed, all resulted in risk estimates of concern (i.e., MOEs < 100).

*Aggregate Risk Assessment*
For the chlorpyrifos aggregate assessment, the EPA has traditionally used a DWLOC approach to calculate the amount of exposure available in the total 'risk cup' for chlorpyrifos in drinking water after accounting for any chloropyrifos exposures from food and residential use. This DWLOC is then compared to the EDWC to determine if there is an aggregate risk of concern. However, because the dietary risks from food exposure alone and from residential exposure alone are of concern, it is not possible to calculate a DWLOC; essentially, the steady state aggregate DWLOC is '0' after accounting for food and residential exposures. Quantitatively aggregating (combining) residential, food, and drinking water exposures would result in risks of concern.

*Occupational Risk Assessment*
Steady state occupational handler and post-application exposure analyses were previously completed for the registered uses of chlorpyrifos. However, occupational exposures and risk estimates have been updated to incorporate the revised PBPK-derived PoDs. The scenarios, assumptions, and exposure inputs have not changed since the previous assessment.

Using the updated PBPK-derived steady state PoDs and uncertainty factors (dermal and inhalation LOC = 100), all agricultural occupational handler scenarios, all primary seed treatment handler scenarios, and all secondary seed treatment (planter) scenarios are of concern with label-specified and maximum levels of personal protective equipment (PPE) or engineering controls (MOEs < 100).

Using the updated PBPK-derived steady state PoDs and uncertainty factors (dermal LOC = 100), all occupational dermal post-application scenarios were of concern on Day 0. The REIs on the registered chlorpyrifos labels range from 24 hours to 5 days. On average, scenarios were not of concern $\geq$ 18 days after treatment.

## 2.0 Use Profile

Chlorpyrifos (0,0-diethyl-0-3,5,6-trichloro -2-pyridyl phosphorothioate) is a broad-spectrum,

chlorinated OP insecticide. 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 adulticide treatments to control mosquitoes. There are also residential uses of roach bait products and ant mound treatments. Permanent tolerances are established (40 CFR§180.342) for the residues of chlorpyrifos in/on a variety of agricultural commodities, including meat, milk, poultry and eggs. There are also tolerances for use in food handling/service establishments (FHE or FSE). Chlorpyrifos is manufactured as granular, microencapsulated liquid, soluble concentrate liquid, water dispersible granular in water soluble packets (WSP), wettable powders in WSPs, impregnated paints, cattle ear tags, insect bait stations and total release foggers. There is a wide range of application rates and methods. The residues of concern for risk assessment purposes are chlorpyrifos and chlorpyrifos oxon under some circumstances.

## 3.0 Tolerance Considerations

See Section 2.0 and Appendix 8 of D22485 (D. Drew *et al.,* 12/29/2014) for details regarding the analytical enforcement method, U.S. tolerances and international residue levels for chlorpyrifos.

## 4.0 Chemical Identity and Physical/Chemical Properties

See Sections 3.1 and 3.2 and Appendix 7 of D22485 (D. Drew *et al.,* 12/29/2014) for details regarding the chemical identity and physical/chemical characteristics of chlorpyrifos.

## 5.0 Hazard Characterization and Dose-Response Assessment

### 5.1 Introduction & Background

Historically, the EPA has used AChE inhibition as the critical effect for deriving risk assessment PoDs for OP pesticides, including chlorpyrifos. However, there is a breadth of information available on the potential adverse neurodevelopmental effects in infants and children as a result of 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 the available neurodevelopmental information. This effort has involved extensive collaboration across the EPA and also within the Federal government.

The stepwise evaluation began with the September 2008 FIFRA SAP. The SAP evaluated the agency's preliminary review of available literature and research on chlorpyrifos, with a particular focus on effects seen in women and children following chlorpyrifos exposures (USEPA, 2008). Subsequently, the agency has developed approaches for risk assessment of semi-volatile pesticides (USEPA, 2009), and developed the draft "Framework for Incorporating Human Epidemiologic & Incident Data in Health Risk Assessment" to better integrate epidemiology data with other types of experimental data in pesticide risk assessments (USEPA, 2010; FIFRA SAP 2010a,b). In early 2011, the FIFRA SAP reviewed the chlorpyrifos physiologically based pharmacokinetic – pharmacodynamic (PBPK-PD) model to conduct quantitative risk assessment.

The model estimates AChE inhibition in humans following exposure to chlorpyrifos and/or the oxon from a variety of exposure pathways (FIFRA SAP 2011).

In 2012, the agency convened another FIFRA SAP to review the latest experimental data related to AChE inhibition, cholinergic and non-cholinergic adverse outcomes, including neurodevelopmental studies on behavior and cognition effects (FIFRA SAP 2012[2]). Similarly, the agency also performed an in-depth analysis of the available chlorpyrifos biomonitoring data and of the available epidemiologic studies from three major children's health cohort studies in the U.S., including those from the Columbia University. The agency also explored plausible hypotheses on mode of actions/adverse outcome pathways (MOAs/AOPs) leading to neurodevelopmental outcomes seen in the biomonitoring and epidemiology studies.

Following the 2012 SAP meeting, the agency solicited additional input from federal experts in the areas of Magnetic Resonance Imaging (MRI) and neurobehavioral testing in children to further clarify results obtained by examination of the epidemiological cohorts.[3] Also, the agency evaluated the potential for chlorpyrifos exposure to lead to the neurobehavioral outcomes seen in the cohorts, and the ability of other environmental exposures to affect the interpretation of the results from the Columbia University studies.

In December, 2014, the agency released "Chlorpyrifos: Revised Human Health Risk Assessment for Registration Review" (herein called "HHRA", D. Drew *et al.,* D424485, 12/29/2014). The 2014 assessment used a PBPK-PD model (Appendix 2) to derive human PoDs based on 10% RBC AChE inhibition; for more information see Appendix 2 of D424485 (D. Drew *et al.,* 12/29/2014). In accordance with the recommendation of the FIFRA SAP (2012), the agency conducted a dose reconstruction analysis based on registered uses available for use in indoor residential areas prior to the year 2000. The highest exposures resulted from the registered broadcast use in residential homes. Based on the output from the PBPK-PD model, for the highest exposure considered (i.e., contact with hard floors following indoor broadcast use of a 1% chlorpyrifos formulation), <10% RBC AChE inhibition in pregnant women and young children would be expected from residential uses. It is noteworthy that all estimates of exposure based on conservative assumptions lead to predicted AChE inhibition levels < 10%. The chlorpyrifos 2014 revised HHRA included retention of the 10X FQPA SF for all populations assessed; including infants, children, youths, and women of childbearing age. The 10X FQPA safety factor was retained based on the conclusion that, given the totality of evidence, chlorpyrifos likely played a role in the neurodevelopmental outcomes reported by the Columbia University investigators but uncertainties, such as the lack of an established MOA/AOP for neurodevelopmental effects and the exposure to multiple AChE-inhibiting pesticides, precluded definitive causal inferences. As a result, there is sufficient uncertainty in the human dose-response relationship for neurodevelopmental effects which prevents the agency from reducing or removing the statutory 10X FQPA SF (D. Drew *et al.,* D424485, 12/29/2014).

In 2013, the EPA sought to obtain the original raw data used to support certain epidemiological analyses of *in* utero exposure to chlorpyrifos and subsequent adverse neurodevelopmental health outcomes in children generated by the CCCEH. While the researchers did not agree to provide

[2] https://www.regulations.gov/docket?D=EPA-HQ-OPP-2012-0040
[3] http://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPP-2008-0850-0170

these data to the EPA, agency staff gained valuable insight into the conduct of the study and the data that were collected in a visit to Columbia University in April 2013. The agency wrote a summary of the 2013 meeting with researchers from Columbia University which can be found in "Appendix 6 Columbia Center for Children's Environmental Health (CCCEH) Epidemiology Data Acquisition "Raw Data Request" of Drew *et. al*, D424485, 12/29/2014. In the summer of 2015, Dr. Dana Barr of Emory University (formerly of CDC) provided the EPA with limited raw urine and blood data in her possession from the three cohorts. However, the files provided from Dr. Barr are not useful for the EPA's current purpose of assessing risk to chlorpyrifos (D. Vogel, Record of Correspondence, 10/2016). The EPA does not have any of the other measurements of the children in the cohort (e.g., chlorpyrifos blood data, interviews, test or IQ scores).

In a 2016 white paper, the agency proposed using data on cord blood reported from the investigators at the Columbia Center for Children's Environmental Health (CCCEH) as the source for new PoDs for risk assessment. This 2016 white paper was reviewed by the FIFRA SAP in April, 2016[4]. The 2016 Panel did not support using the CCCEH chlorpyrifos concentrations in cord blood quantitatively to derive PoDs for risk assessment. The Panel noted a number of uncertainties, including: the use of results from a single longitudinal study without replication from another cohort; the lack of verification and replication of the analytical chemistry results that reported very low levels of chlorpyrifos (pg/g); and the lack of raw data available for independent evaluation. Importantly, however, the Panel agreed that "both epidemiology and toxicology studies suggest there is evidence for adverse health outcomes associated with chlorpyrifos exposures below levels that result in 10% red blood cell (RBC) acetylcholinesterase (AChE) inhibition (i.e., toxicity at lower doses)." Moreover, the Panel did support the use of the PBPK model to assess internal dosimetry from various exposure scenarios. The SAP specifically stated that PBPK modelling "is a valuable tool to interpret the biomonitoring data in circumstances where multiple routes of exposure occur and when based on best available information as inputs."

Therefore, based on the evidence collected from 2014 to date, as summarized above, the agency has updated its HHRA for the existing uses of chlorpyrifos. This 2016 human health risk assessment provides limited, summary information and substantially relies on previous documents developed for chlorpyrifos which contain more detailed evaluations of scientific literature and the PBPK model:

- D. Drew *et al.,* Chlorpyrifos: Revised Human Health Risk Assessment for Registration Review, December 29, 2014, D424485; and
- U.S. Environmental Protection Agency, Literature Review on Neurodevelopment Effects & FQPA Safety Factor Determination for the Organophosphate Pesticides, September 15, 2015, D331251.

### 5.2 Summary of the Literature Review on Neurodevelopmental Effects

Detailed summaries of the epidemiological studies used in this literature review can be found either in the 2014 chlorpyrifos HHRA (D. Drew *et al.,* D424485, 12/29/2014), the 2015 literature review for other organophosphates (OPP/USEPA, D331251, 09/15/2015), and reviews of newer studies (E. Holman, D432184, 03/25/2016). Only brief summaries of the literature reviews are

[4] https://www.regulations.gov/docket?D=EPA-HQ-OPP-2016-0062

provided below.

Newer lines of research on OPs have raised some uncertainty about the agency's risk assessment approach of using AChE inhibition for deriving PoDs. These uncertainties are in the areas of potential AOPs; *in vivo* animal studies; and notably results seen in epidemiological studies in mothers and children, with regard to the potential for neurodevelopmental effects in fetuses and children. Many of these studies have been the subject of review by the agency over the last several years as part of the development of the 2014 chlorpyrifos HHRA (D. Drew *et al.,* D424485, 12/29/2014).

A review of the scientific literature on potential MOAs/AOPs[5] leading to effects on the developing brain was conducted for the 2012 FIFRA SAP meeting (USEPA, 2012) and updated for the December 2014 chlorpyrifos HHRA (D. Drew *et al.,* D424485, 12/29/2014). In short, multiple biologically plausible hypotheses and pathways are being pursued by researchers that include targets other than AChE inhibition, including cholinergic and non-cholinergic systems, signaling pathways, proteins, and others. However, no one pathway has sufficient data to be considered more credible than the others. Published and submitted guideline developmental neurotoxicity (DNT) laboratory animal studies have been reviewed for OPs (D. Drew *et al.,* D424485, 12/29/2014 and USEPA, D331251, 09/15/2015). Neurobehavioral alterations in laboratory animals were often reported; however, at AChE inhibiting doses. Moreover, there was generally a lack of consistency in pattern, timing, and dose-response for these effects; and a number of studies were of low quality. However, the information on neurobehavioral effects as a whole provides evidence of long-lasting neurodevelopmental disorders in rats and mice following gestational exposure to OPs.

Initially, the agency focused on epidemiological studies from three US cohorts: 1) The Mothers and Newborn Study of North Manhattan and South Bronx performed by the 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;" and 3) the Center for Health Assessment of Mothers and Children of Salinas Valley (CHAMACOS) conducted by researchers at University of California Berkeley. The agency has evaluated these studies and sought external peer review (FIFRA SAP reviews in 2008 and 2012; federal panel, 2013[6]) and concludes they are of high quality. In the three US epidemiology cohort studies, mother-infant pairs were recruited for the purpose of studying the potential health effects of environmental exposures during pregnancy on subsequent child development. Each of these cohorts has evaluated the association between prenatal chlorpyrifos and/or OP exposure with adverse neurodevelopmental outcomes in children through age 7-11 years. For the 2014 chlorpyrifos HHRA (D. Drew *et al.,* D424485, 12/29/2014), the EPA included epidemiologic research results from these three US prospective birth cohort studies but primarily focused on the results of CCCEH since this cohort has published studies on the association between cord blood levels of chlorpyrifos and neurodevelopmental outcomes. The agency retained the FQPA 10X SF in the 2014 chlorpyrifos revised risk assessment, in large part, based on the findings of these studies.

[5] 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.
[6] http://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPP-2008-0850-0170

In the 2015 updated literature review (USEPA, D331251, 09/15/2015), the agency conducted a systematic review expanding the 2012/2014 review which was focused only on US cohort studies with particular emphasis on chlorpyrifos. The expanded 2015 review includes consideration of the epidemiological data on any OP pesticide, study designs beyond prospective cohort studies, and non-U.S. based studies. The updated literature review identified seven studies which were relevant (Bouchard *et al.,* 2010; Fortenberry *et al.,* 2014; Furlong *et al.,* 2014; Guodong *et al.,* 2012; Oulhote and Bouchard, 2013; Zhang *et al.,* 2014; Shelton *et al.,* 2014). These seven studies have been evaluated in context with studies from the 2012/2014 review (D. Drew *et al.,* D424485, 12/29/2014). In addition, the agency has also reviewed more recent studies from CCCEH (Rauh *et al.*, 2015) and a pooled analysis of U.S. cohort studies (Engel *et al.*, 2015) (E. Holman, D432184, 03/25/2016). As discussed below, Rauh *et al.* (2015) provides further evidence of neurodevelopmental outcomes in the CCCEH study. The Engel *et al.* (2015) study shows relatively consistent results compared to previous studies conducted at 24 months (Engel *et al.*, 2011; Rauh *et al.*, 2006). Only a brief summary of this review is provided below. The agency continues to conclude that the 3 U.S. cohort studies (CCCEH, CHAMACOS, and Mt. Sinai) provide the most robust available epidemiological evidence.

The agency acknowledges the lack of established MOA/AOP pathway, the inability to make strong causal linkages, and the unknown window(s) of susceptibility. These uncertainties do not undermine or reduce the confidence in the findings of the epidemiology studies. The epidemiology studies reviewed in the 2012/2014 and 2015 literature reviews represent different investigators, locations, points in time, exposure assessment procedures, and outcome measurements. Despite differences in study design, with the exception of two negative studies in the 2015 literature review (Guodong *et al.,* 2012; Oulhote and Bouchard, 2013) and the results from the more recent Engel *et al.* (2015) study[7], all other study authors have identified associations with neurodevelopmental outcomes associated with OP exposure; these conclusions were across four cohorts and twelve study citations. Specifically, 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 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.

The CCCEH study primarily tested for the presence of chlorpyrifos in cord blood, and therefore remains the most relevant for the purposes of chlorpyrifos risk assessment. As summarized above, when comparing high to low exposure groups at 3 years of age in the CCCEH study (Rauh *et al.*, 2006), there were increased odds of:

- Mental delay (odds ratio; OR=2.4; 95% Confidence interval (CI): 1.1–5.1);
- Psychomotor delay (OR=4.9; 95% CI: 1.8–13.7);
- Attention disorders (OR=11.26; 95% CI: 1.79–70.99);
- Attention deficit hyperactivity disorder (ADHD) (OR=6.50; 95% CI: 1.09–38.69); and
- Pervasive Developmental Disorders (PDD) (OR=5.39; 95% CI: 1.21–24.11).

In a follow-up study at age 11, CCCEH study authors observed increased odds of mild to

[7] It is noted that the CCCEH study participants included in the Engel et al (2015) study are women enrolled from 2000-2001, i.e. after the cancellation of the residential uses of chlorpyrifos.

moderate tremor when comparing high to low exposure groups (Rauh *et al.*, 2015). Rauh *et al.,* (2011) evaluated relationship between prenatal chlorpyrifos exposure and neurodevelopment in 265 of the CCCEH cohort participants at age 7 years. They described the log of Working Memory Index (WMI) of children as linearly associated with concentration of chlorpyrifos (CPF) in cord blood: Slope = -0.006 (95% CI = -0.01, -0.002). For each standard deviation increase in exposure (4.61 pg/g), they observed a 1.4% reduction in Full-Scale IQ and a 2.8% reduction in Working Memory.

In summary, the EPA's assessment is that the CCCEH study, with supporting results from the other 2 U.S. cohort studies and the seven additional epidemiological studies reviewed in 2015, provides sufficient evidence that there are neurodevelopmental effects occurring at chlorpyrifos exposure levels below that required for AChE inhibition.

## 5.3 Dose-Response Assessment

### 5.3.1 Conceptual Approach

As noted above, the agency has historically used 10% inhibition of RBC AChE as the critical effect for deriving PoDs for chlorpyrifos and other OPs. For example, the 2014 HHRA on chlorpyrifos used the PBPK-PD model to derive PoDs that could result in 10% RBC AChE inhibition for multiple exposure scenarios (e.g., worker, dietary, residential). While significant uncertainties remain about the actual exposure levels experienced by mothers and infant participants in the children's health cohorts, it is unlikely that these exposures resulted in RBC AChE inhibition at or above the 10% AChE inhibition response level. For example, as part of the CHAMACOS study, Eskenazi *et al.,* (2004) measured AChE activity and showed that no inhibition in AChE activity were observed. Additionally, following the recommendation of the FIFRA SAP in 2012, the agency conducted a dose reconstruction analysis for pregnant women and young children based on registered residential chlorpyrifos uses available prior to 2000 inside the home (D. Drew *et al.,* D424485, 12/29/2014). The PBPK-PD model using this dose reconstruction analysis indicates that for the highest exposure considered (i.e., indoor broadcast use of a 1% chlorpyrifos formulation), <1% RBC AChE inhibition was produced in pregnant women. While uncertainty exists as to actual chlorpyrifos exposure at (unknown) critical windows of exposure, the agency believes it is unlikely individuals in the epidemiology studies experienced RBC AChE inhibition from their exposure to chlorpyrifos. The 2016 SAP concluded that "epidemiology and toxicology studies suggest there is evidence for adverse health outcomes associated with chlorpyrifos exposures below levels that result in 10% RBC AChE inhibition (i.e., toxicity at lower doses)." As such, the use of 10% RBC AChE inhibition for deriving PoDs for chlorpyrifos may not provide a sufficiently protective human health risk assessment. Therefore, the agency has endeavored to derive PoDs and uncertainty/safety factors for risk assessment that are protective of both the AChE inhibition and any adverse effects that could occur at lower doses.

As noted, however, the 2016 SAP did not support using the CCCEH cord blood quantitatively in deriving revised PoDs. In their verbal comments, multiple panelists suggested a 'hybrid' approach. In the written report, the SAP did not provide a suggested approach for how the EPA might continue to use the epidemiology data results in a quantitative risk assessment without

attempting to derive the PoD from cord blood data. Specifically, the SAP stated that, given the absence of a particular key window of exposure for the effects shown in the CCCEH study, the EPA should use estimated peak blood concentrations or TWA blood concentrations within the prenatal period as the PoD rather than blood concentrations at delivery. The Panel was also positive and supportive of the agency's use of the PBPK model as a tool for assessing internal dosimetry from the typical OPP exposure scenarios using peer reviewed exposure assessment approaches (e.g., food, water, residential, worker). As such, use of the PBPK model coupled with the typical OPP exposure scenarios to derive PoDs based on TWA blood concentrations, as recommended by the SAP, provide the strongest scientific foundation for moving forward in human health risk assessment for chlorpyrifos. This approach:

- incorporates peer reviewed and accepted inputs for both chlorpyrifos and standard pesticide risk assessment, including: the Residential SOPs[8], the EPA Exposure Factors Handbook 2011 Edition, chlorpyrifos-specific residential exposure modeling inputs and others;
- does not directly rely on quantitative measures of chlorpyrifos in cord blood obtained from the CCCEH, which were the source of uncertainty identified by the 2016 SAP, while still accepting the qualitative findings that chlorpyrifos contributed to the outcomes reported by the CCCEH, which were supported by the 2008 and 2012 SAPs; and
- does not directly rely on quantitative measures of chlorpyrifos in cord blood obtained from the CCCEH, and thus, the lack of access to the raw data from the CCCEH is less of an uncertainty.

The following sections describe the use of the PBPK model to 1) predict TWA of blood concentrations from an exposure scenario likely to be experienced by women in the CCCEH study (indoor use of chlorpyrifos-containing products), and 2) determine the external doses (PoDs for risk assessment) for infants, children, youths, and adults using current exposure assumptions and methodologies (i.e., The 2012 Residential SOPs, and chemical-specific exposure data, etc.) that result in the predicted TWA of blood concentration. The likely indoor use scenario which was experienced by the women in the CCCEH study was derived from the indoor crack and crevice uses of chlorpyrifos; reasoning for selecting this specific scenario is detailed below.

### 5.3.2 Deriving Internal Concentrations of Chlorpyrifos from Indoor, Crack & Crevice Use

In order to derive a protective PoD for risk assessment from the internal concentrations of chlorpyrifos, the agency reviewed the chlorpyrifos registered uses that would have been available to the CCCEH cohort. The following two risk mitigation actions were the basis for the agency's conclusion that the crack and crevice uses of chlorpyrifos was the most appropriate scenario to assess exposure to the women in the CCCEH cohort in the approximate 1998-2000 timeframe:

- In January 1997, the technical registrants agreed to cancel all broadcast and total release/aerosol foggers containing chlorpyrifos in order to reduce indoor exposures, especially to children and other sensitive groups. The following chlorpyrifos uses were

[8] https://www.epa.gov/sites/production/files/2015-08/documents/usepa-opp-hed_residential_sops_oct2012.pdf

also cancelled: all direct application of pet products including sprays, shampoos, and dips (pet collars not included); and all insecticidal paint additives. Further, all concentrates which required mixing were eliminated, limiting the household consumer's access to only ready-to-use products. Although the above uses were cancelled in 1997, existing stocks could be phased out, or applied until depleted. Indoor crack and crevice (perimeter) and spot treatment as a termiticide uses of chlorpyrifos continued to be registered.

- In June 2000, the technical registrants of chlorpyrifos, agreed to eliminate or phase out nearly all remaining uses that resulted in residential exposure, including: home lawn, crack and crevice, and other indoor uses. Non-residential uses where children could be exposed, such as schools and parks, were also cancelled, with the exception of roach and ant baits in child resistant packaging, and mosquito and fire ant control. For uses that were cancelled, retailers had a stop sale date of December 31, 2001. A phase out of existing stocks was allowed following the 2001 stop sale.

Additionally, in the summer of 2016, OPP contacted several professional pesticide applicators working in New York City apartment buildings around the time of the CCCEH cohort. These professional pesticide applicators recalled that the crack and crevice[9] use was the predominant use around 1998-2000 (D. Friedman, Record of Correspondence, 10/2016). Based on this input, and the mitigation rationale outlined above, the agency has focused on crack and crevice exposures for the 2016 risk assessment.

The 2012 FIFRA SAP (2012) recommended that the EPA conduct a "dose reconstruction" analysis of indoor residential uses to assess potential for RBC AChE inhibition. The dose reconstruction analysis was conducted and presented in the 2014 HHRA[10]. The goal of the dose reconstruction exercise was to estimate upper limit, bounding level exposures, to test the hypothesis of whether RBC AChE at or above the 10% inhibition level used by the agency for typical AChE PoDs may have occurred in the CCCEH cohort. For example, in the dose reconstruction analysis, exposure to the women was assumed to occur 24 hours a day without adjustments for bathing, showering, or leaving the residence for 14 consecutive days. For the 2014 HHRA, residential handler and post-application exposures from indoor broadcast applications resulted in the highest risk estimates and, therefore, were the only exposure estimates presented. The purpose of 2016 analysis for this risk assessment is to predict typical product usage and behaviors thereby deriving more accurate and realistic estimates of exposure compared to the 2014 analysis.

For the 2016 risk assessment, the agency has assessed chlorpyrifos exposures resulting from post-application exposures only. Whyatt *et al.* (2002) reported that many women applied pesticide products themselves, and that majority who reported using pesticide products used them at least once per month. However, as the agency has shown in the 2014 dose reconstruction analysis, post-application exposures are greater in magnitude than exposures which occur during an application. Therefore, the assessment of post-application exposure ensures that the highest potential exposures are evaluated. Specifically, the 2016 risk assessment

[9]Per the 2012 Residential SOPs, a crack and crevice application is defined as application of pesticides with the use of a pin stream nozzle, into cracks and crevices in which pests hide or through which they may enter a building. Such openings commonly occur at expansion joints, between different elements of construction, and between equipment and floors.

[10] The methods, algorithms, and exposure data used to conduct the dose reconstruction analysis can be referenced in Appendix 10 of the 2014 HHRA.

focuses on the post-application exposures from the chlorpyrifos in crack and crevice use since this was the predominant application type during the time of the CCCEH cohort.

The dose reconstruction in the 2016 risk assessment is based on the methods outlined in the 2012 Residential SOPs[11] which describe specific algorithms and inputs, on a scenario-specific basis.[12] Appendix 10 of the 2014 HHRA (D. Drew *et al.,* D424485, 12/29/2014) can be referenced for a description of the methods, algorithms, and inputs used. Specifically, the 2012 Residential SOPs[13] have been used to predict the range of potential exposures which could have occurred to individuals in the cohort for crack and crevice hard surface and carpet treatments. The present analysis uses the same chemical-specific exposure data inputs recommended in the 2012 Residential SOPS (*i.e.*, the fraction of chlorpyrifos residues transferred from treated carpet and hard surfaces to the exposed individual; and exposure data used to derive the liquid formulation transfer coefficient (TC)). Additionally, chemical-specific exposure data were used to define the concentrations of chlorpyrifos present in air following indoor applications. The differences between the previous dose reconstruction and the present analysis are: (1) the exposure duration was 24 h/day for the 2014 dose reconstruction analysis, and 2 h/day for the present analysis; (2) predicted endpoint for the dose reconstruction analysis was the peak RBC AChE inhibition level during the 14 days post-application, and the predicted endpoint for the present analysis was time-weighted average of chlorpyrifos concentrations in blood; (3) no shower was assumed to occur over the 14-day exposure period for the dose reconstruction analysis, whereas a daily shower is assumed to occur for the present analysis; (4) the total exposure duration was 14 days in the dose reconstruction analysis, and 30 days in the present analysis. The assumption that women followed in the CCCEH cohort showered immediately after exposure leads to significantly more conservative estimates of risk assessment PoDs (i.e., neurodevelopmental effects may have occurred at lower exposure levels when assuming that the women showered after daily exposure vs. when it is assumed that the women did not shower after daily exposure); however, since other inputs (e.g., 50% of the body exposed) lead to less conservative PoD estimates, the combination of inputs used to estimate exposures is expected to reasonably approximate exposures to these women resulting in reasonable risk assessment PODs.

For the 2016 risk assessment, the agency assumed a once daily shower occurred immediately following exposure activities. The PBPK model simulation were conducted for a 30-day post-application in the crack & crevice scenario. Daily exposure durations for post-application dermal contact with carpets and hard surfaces were selected based on the recommendation in the 2012 Standard Operating Procedures for Residential Pesticide Exposure Assessment[14] (herein referred to as the 2012 Residential SOPs). Specifically, for adults, the recommended exposure durations for post-application dermal contact are 8 and 2 hours daily for carpets and hard surfaces, respectively. These values are based on the EPA Exposure Factors Handbook 2011[15] Edition that provides information on the total time spent in a residence and time spent in various rooms within a residence. The hard surface exposure scenario resulted the highest estimated exposures and, therefore, was selected for PBPK model PoD derivation. Additionally, chlorpyrifos residues were assumed to dissipate 10% daily; that is, the total amount of residue

[11] https://www.epa.gov/sites/production/files/2015-08/documents/usepa-opp-hed_residential_sops_oct2012.pdf
[12] The 2012 Residential SOPs were subjected to peer review by FIFRA SAP in October 2009. http://www.regulations.gov/#!docketBrowser;rpp=50;po=0;D=EPA-HQ-OPP-2009-0516
[13] https://www.epa.gov/sites/production/files/2015-08/documents/usepa-opp-hed_residential_sops_oct2012.pdf
[14] http://www.epa.gov/pesticides/science/residential-exposure-sop.html
[15] http://cfpub.epa.gov/ncea/risk/recordisplay.cfm?deid=236252

available for transfer from the treated floor is assumed to reduce by 10% for each subsequent day of exposure until the end of the 30th day prior to the next application. The 10% value was based on an evaluation of all available chlorpyrifos-specific floor residue data. For all post-application exposure scenarios a female bodyweight reflective of all trimesters of pregnancy, 75 kg, was assumed to reflect the population of interest from the CCCEH cohort. This value was derived from the EPA Exposure Factors Handbook 2011 Edition (adult female: Tables 8-3 through 8-5; body weight of pregnant women: Table 8-29).

The results of the 2016 dose reconstruction assessment of the post-application exposures following contact with hard surfaces following indoor chlorpyrifos crack and crevice treatment is presented in Table 5.3.2.

**Table 5.3.2. Residential Post-application Exposures to Women in the CCCEH Cohort Following Indoor Chlorpyrifos Crack and Crevice Treatment.**

| Exposure Scenario | Formulation | Deposited Residue[1] (µg/cm²) | Fraction Transferred[2] | Transferable Residue[3] (µg/cm²) | Transfer Coefficient (cm²/hr) | Exposure Time (hr/day) | Dermal Dose[4] (mg/kg/day) | Airborne Concentration of Chlorpyrifos[5] (mg/m³) - Day of Application |
|---|---|---|---|---|---|---|---|---|
| Crack and Crevice (Hard Surfaces) | 1% PCO Crack and Crevice Application | 0.30 | 0.13 | 0.039 | 6,800 | 2 | 0.00707 | 0.00089 |

1 Estimated based on the recommendations of the 2012 Residential SOPs: Indoor Environments SOP.
2 Chlorpyrifos-specific fraction transfer as recommended in the 2012 Residential SOPs: Indoor Environments SOP (Table 7-9; Arithmetic Mean).
3 Transferable Residue (µg/cm²) = Deposited Residue (µg/cm²) * Fraction Transferred (unitless)
4 Dermal Dose (mg/kg/day) = Transferable Residue (µg/cm²) * Transfer Coefficient (cm²/hr) * Exposure Time (hr/day) * Conversion Factor (0.001 mg/µg)
5 Average airborne concentration of chlorpyrifos from crack and crevice on the day of product application as determined from 3 literature studies and 1 registrant submitted study.

The PBPK model-predicted time course of chlorpyrifos concentrations in blood based on the crack and crevice scenario is provided in Figure 1. The predicted TWA of chlorpyrifos concentration in blood from this scenario was 0.004 µg/L, shown as the solid horizontal line in Figure 1.

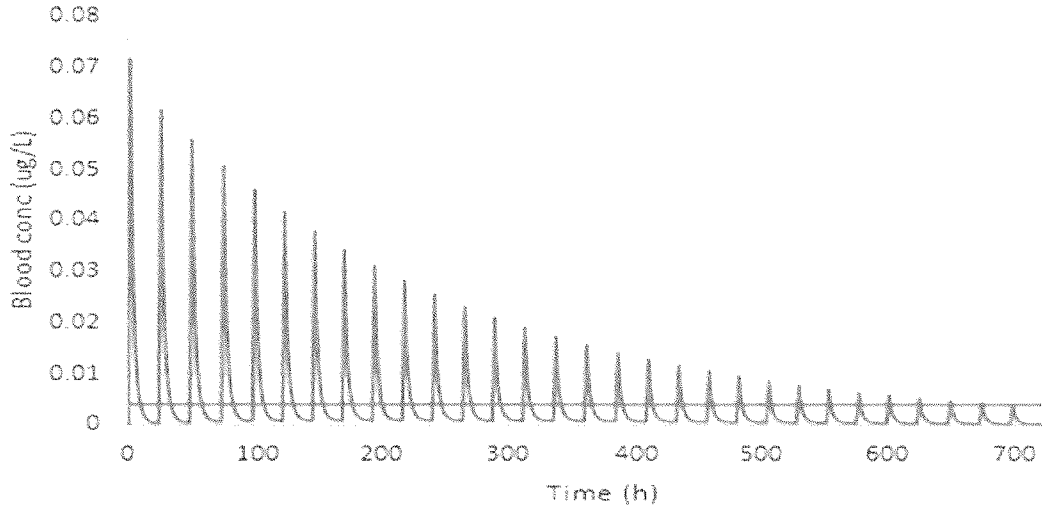


**Figure 1:** The PBPK model-predicted time course of chlorpyrifos concentrations in blood based on the crack and crevice scenario. The predicted TWA of chlorpyrifos concentration in blood (0.004 µg/L) is shown by the solid line.

### 5.3.3 Determining PoDs

In typical risk assessments, PoDs are derived directly from laboratory animal studies and inter- and intra-species extrapolation is accomplished by use of 10X factors. In the case of chlorpyrifos, the PBPK model for chlorpyrifos was used as a data-derived extrapolation approach to estimate individual PoDs for pregnant women and children. As noted above, the PBPK model was first used to predict, from the crack and crevice post-application scenario, the TWA of chlorpyrifos concentration in blood as the internal dose metric for deriving PoDs in the subsequent analyses.

For the 2014 HHRA (D. Drew *et. al*, D424485, 12/29/2014), the EPA developed PoDs based on AChE inhibition to protect against cholinergic toxicity; such cholinergic toxicity could occur to any lifestage if exposure is sufficiently high. As such, in 2014, the EPA evaluated the spectrum of lifestages from the fetus through adulthood. Fetuses may be exposed to chlorpyrifos through the mother while infants and children may be exposed directly. Studies in laboratory animals do not suggest any specific critical period or lifestage, but instead suggest pre- and post-natal periods of susceptibility. The EPA acknowledges that the epidemiology literature regarding associations between post-natal (infancy, childhood) biomarker metrics and neurodevelopmental outcomes is limited to the Bouchard *et al.,* (2010) study, a cross-sectional study that observed positive association between attention and behavior problems and total dialkyl phosphate metabolites (DAPs) and dimethyl alkylphosphate metabolites (DMAPs), using urinary National Health and Nutrition Examination Survey (NHANES) data in children 8–15 years old. The other studies which evaluated postnatal biomarker metrics and neurodevelopment outcomes have found no statistically significant associations. Specifically, postnatal exposure to OPs (measured as DAPs) has been assessed in the CHAMACOS cohort (Eskenazi *et al.*, 2007; Young *et al.*,

2005; Bouchard *et al.*, 2011), two other cross-sectional studies (Guodong *et al.*, 2012; Oulhote and Bouchard, 2013) and Engel *et al.*, (2016). Despite the limited epidemiological evidence from postnatal exposure, the EPA is proposing to use the TWA as the most relevant source of information for deriving a PoD specific for chlorpyrifos for fetuses, infants, and children. Consistent with the advice from the 2016 SAP, the EPA believes that the CCCEH results are directly relevant to fetal exposure and newborns; however, the EPA acknowledges they may be less relevant to older infants, toddlers, and children. The EPA has conducted exposure assessments for all typical age groups for completeness and acknowledges that the exposure and risk assessment results for females 13-49 years old are the most relevant to the CCCEH data.

The PBPK model accounts for pharmacokinetic characteristics to derive age, duration, and route specific PoDs (Table 5.3.3.3). Separate PoDs have been calculated for dietary (food, drinking water), residential, and occupational exposures by varying inputs on types of exposures and populations exposed to obtain a predicted time-weighted average of 0.004 µg/L chlorpyrifos in blood using inputs specific to each scenario (i.e., duration exposed, amount consumed, etc). Specifically, the following characteristics have been evaluated: route (dermal, oral, inhalation); body weights which vary by life-stage; exposure duration (hours per day, days per week); and exposure frequency [events per day (eating, drinking)].

To derive a PoD for each non-dietary and dietary exposure scenario and subpopulation, the appropriate body weight for each age group or sex was taken from the Exposure Factors Handbook (USEPA, 2011) (for occupational exposures) or from the NHANES/What We Eat in America (WWEIA) Survey[16] (for dietary exposures). All body weights used are consistent with those assumed for typical pesticide dietary, occupational, and residential exposure assessments and shown in Table 5.3.3.1.

**Table 5.3.3.1. Body Weight Assumptions Incorporated into PBPK Model for Chlorpyrifos.**

| Exposure Scenario | Exposure Pathway | Population & Body Weight (kg) | | | | |
|---|---|---|---|---|---|---|
| | | 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) |
| Dietary | Food and Drinking Water | 4.8[1] | 12.6[2] | 37.1[2] | 67.3[2] | 72.9[2] |
| Residential (Golfers) | Dermal | | | 32[5] | 57[6] | 69[4] |
| Residential (Mosquitocide Application) | Dermal, Oral, Inhalation | | 11[3] | | | |
| Residential (Bystander/ Volatilization Assessment) | Inhalation | | 11[3] | | | |
| Occupational | Dermal, Inhalation | | | | | |

1 For infants from birth to < 1 year old, the agency has selected the body weight for the youngest age group, birth to < 1 month old, 4.8 kg (Exposure Factors Handbook, Table 8-3, mean body weight for the birth to < 1 month age group).
2 NHANES/WWEIA
3 Exposure Factors Handbook, Table 8-3, mean body weight for the 1 to < 2 year old age group.

[16] http://www.ars.usda.gov/Services/docs.htm?docid=13793

4 Exposure Factors Handbook, Table 8-5, mean body weight for females 13 to < 49 years old.
5 Exposure Factors Handbook, Table 8-3, mean body weight for the 6 to < 11 year old age group.
6 (Exposure Factors Handbook, Table 8-3, mean body weight for the 11 to < 16 year old age group).

Table 5.3.3.2 shows the durations (days) of exposure included in the PBPK model to derive PoDs.

**Table 5.3.3.2. Days of Exposure Assumptions Incorporated into PBPK Model for Chlorpyrifos.**

| Exposure Scenario | Exposure Pathway | Population & Days of Exposure | | | | |
|---|---|---|---|---|---|---|
| | | 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) |
| Dietary | Food and Drinking Water | 21 | 21 | 21 | 21 | 21 |
| Residential (Golfers) | Dermal | | | 21 | 21 | 21 |
| Residential (Mosquitocide Application) | Dermal, Oral, Inhalation | | 21 | | | |
| Residential (Bystander/ Volatilization Assessment) | Inhalation | | 1 & 21 | | | |
| Occupational | Dermal, Inhalation | | | | | |

To derive the dietary exposure PoDs, dietary exposure was estimated daily for 21 days. For drinking water exposures, the daily water consumption volume was set to 0.688557 L for infants, children between 1-2 year old, and children 6-12 years old; 1.71062 L for youths 13-19 years old and female adults. Infants and children were assumed to consume water six times a day; youths and female adults were assumed to consume water four times a day. For food exposures, the eating event was set to one meal per day. The daily volumes consumed and number of daily consumption events for all populations are mean values by age group based on USDA's WWEIA. The mean daily water consumption amounts for children 1- 2 years old (0.35 L) and children 6-12 years old (0.58 L), were less than that for infants (0.688557 L); the infant daily water consumption volume was selected for all child sub-populations to be protective. For youths 13-19 years old, the mean daily water consumption amount (0.93 L) was less than that for the female adults (1.71062 L); therefore, the adult daily water consumption was selected for both subpopulations to be protective.

For all residential dermal exposures to chlorpyrifos, the fraction of skin in contact with chlorpyrifos was set to 50% to reflect uncovered skin areas for adults and children wearing shorts and a tee shirt. A daily shower (i.e., washing off the chlorpyrifos) was assumed immediately 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 ground applications and 1 hour for aerial applications. For residential inhalation exposures following public health mosquitocide application, the exposure duration was set to 1 hour per

day. These exposure times selected were based on those recommended in the 2012 Residential SOPs. For residential bystander exposures from volatilization following treatment of nearby fields, the inhalation exposure time was set to 24 hours per day. For inhalation exposures following mosquitocide application and from volatilization, the inhalation rates were set to 0.33 $m^3$/hour for children 1 to < 2 years old and 0.64 $m^3$/hour for adults.

In addition to dietary and residential exposures, the PBPK model was also used to estimate PoDs resulting in a time-weighted average of 0.004 µg/L chlorpyrifos in blood following occupational exposures (Table 5.3.3.3). Dermal exposures for workers assumed even distribution across the entire body surface area. A daily shower (i.e., washing off the chlorpyrifos) was assumed following chlorpyrifos exposure. The worker was assumed to be a female adult between the ages of 13 to 49, and had a body weight of 69 kg. This worker is exposed to chlorpyrifos either via inhalation or skin for 8 hours/day, 5 days/week, for a total of 21 days.

**Table 5.3.3.3. PBPK Model-Predicted Chlorpyrifos Point of Departures (PoDs) Corresponding to a Time-Weighted Average of 0.004 µg/L Chlorpyrifos in Plasma*.**

| Exposure Scenario | Exposure Pathway | Infants ( < 1 year 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) |
|---|---|---|---|---|---|---|
| Dietary | Drinking Water (µg/kg/day) | 1.4 | 3.2 | 7.1 | 4.8 | 5.1 |
| | Food (µg/kg/day) | 0.2 | 0.17 | 0.13 | 0.12 | 0.12 |
| Residential (Golfers) | Dermal (µg/kg/day) | | | 2.2 | 1.4 | 1.3 |
| Residential (Mosquitocide Application) | Dermal (µg/kg/day) | | 14.9 | | | 3.4 |
| | Oral (µg/kg/day) | | 0.17 | | | |
| | Inhalation (concn. in air mg/$m^3$)[1] | | *Aerial:* 0.00165 *Ground:* 0.0011 | | | *Aerial:* 0.0051 *Ground:* 0.0034 |
| Residential (Bystander/ Volatilization Assessment) | Inhalation (concn. in air mg/$m^3$) | | *Steady State:* 0.00068 *Acute:* 0.0013 | | | *Steady State:* 0.00021 *Acute:* 0.004 |
| Occupational | Dermal (µg/kg/day) | | | | | 0.47 |
| | Inhalation (concn. in air mg/$m^3$) | | | | | 0.0011 |

*PoDs and exposure and risk estimates for females 13-49 yrs covers all youths >13 yrs.
1. PBPK model inputs for inhalation mosquitocide scenarios differ based on the exposure scenario being assessed. Since the AgDISP (v8.26) model predicts the 1 hour average air concentration following aerial applications, the PBPK-PD was model was run assuming 1 hr of inhalation exposure/day, 7 days/week, and 21 days of exposure. For ground based ULV applications, risks are estimated based on the inhalation exposure duration for time spent outdoors (1.5 hours/day) and, therefore, the PBPK-PD model was run assuming 1.5 hours of inhalation exposure/day, 7 days/week, 21 days of exposure.

### 5.3.4 Uncertainty, Extrapolation, & FQPA Safety Factors

The TWA blood level resulting from chlorpyrifos exposure from the crack and crevice scenario

is considered a LOAEL rather than a NOAEL, since this is the exposure level likely to be associated with neurodevelopmental effects reported in the CCCEH study. In situations where the agency selects a PoD from a study where a NOAEL has not been identified, the EPA generally will retain the FQPA SF of 10X to account for the uncertainty in using a LOAEL. In the 2016 revised risk assessment this is being done for chlorpyrifos. The 2016 revised risk assessment also applies a 10X uncertainty factor for intraspecies variability because of the lack of sufficient information to reduce or remove this factor. Typically, the agency uses animal studies for selection of PoDs and, as such, retains a 10X interspecies factor for extrapolation of the animal data to assess human health. However, with use of the PBPK-PD model which accounts for the pharmacokinetic and pharmacodynamic differences between animals and humans to derive PoDs, it is appropriate to reduce the interspecies factor to 1X. Therefore, the total uncertainty factors for chlorpyrifos in this 2016 risk assessment are 100X (10x for intra-species extrapolation and 10x for the FQPA 10 safety factor).

## 6.0 Dietary Exposure and Risk Assessment

HED had previously conducted both acute and steady state dietary (food only) exposure analyses for chlorpyrifos using DEEM and Calendex software with the Food Commodity Intake Database (FCID) (D. Drew *et al.,* D424486, 11/18/2014), respectively.

For the current assessment, the steady state exposure values resulting from the 2014 dietary assessment are compared to the updated PBPK-derived steady state Population Adjusted Dose (ssPAD). When the dietary exposure exceeds 100% of the ssPAD there is a potential risk concern.

Since the steady state dietary assessment is protective of any acute food exposures, only the results of the steady state assessment are discussed herein. The steady state analysis calculated exposures for the sentinel populations of infants <1 year old, children 1-2 years old, youth 6-12 years old, and females 13-49 years old.

All details pertaining to the assumptions, data inputs, and exposure outputs for the dietary analysis may be found in the 2014 dietary assessment memorandum (D. Drew *et al.,*D425586, 11/18/2014).

### 6.1 Food Residue Profile

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 the available crop field trials, metabolism studies, and PDP monitoring, the cholinesterase inhibiting metabolite, chlorpyrifos oxon, would be not be present in edible portions of the crops, or in livestock tissue or milk and, therefore, is not included in the food assessment.

The steady state dietary exposure analysis is 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 residues or tolerance level residues were assumed. The Biological & Economic Analysis Division (BEAD) provided

percent crop treated information in the Screening Level Usage Analysis (SLUA; May 1, 2014). Food processing factors from submitted studies were used as appropriate. All commodities with current U.S. tolerances for residues of chlorpyrifos are included in this assessment (40 CFR§180.342).

### 6.2 Steady State Dietary (Food Only) Exposure and Risk Estimates

The steady state dietary (food only) exposures for chlorpyrifos are of concern at the 99.9$^{th}$ percentile of exposure for all population subgroups analyzed. Children (1-2 years old) is the population subgroup with the highest risk estimate at 14,000% of the $ssPAD_{food}$.

**Table 6.2. Steady State Dietary (Food Only) Exposure and Risk Estimates for Chlorpyrifos.**

| Population Subgroup | ss $PoD_{food}$[1] (µg/kg/day) | $ssPAD_{food}$[2] (µg/kg/day) | Food Exposure[3] (µg/kg/day) | % of $ssPAD_{food}$ |
|---|---|---|---|---|
| Infants (< 1 yr) | 0.20 | 0.002 | 0.186 | 9,300 |
| Children (1-2 yrs) | 0.17 | 0.0017 | 0.242 | 14,000 |
| Youths (6-12 yrs) | 0.12 | 0.0012 | 0.128 | 11,000 |
| Adults (Females 13-49 yrs) | 0.12 | 0.0012 | 0.075 | 6,200 |

1 Steady state point of departure; daily dose predicted by PBPK-PD for steady state (21 day) dietary (food) exposures (see Table 5.3.3.3 for PoDs).
2 ssPAD= Steady state population adjusted dose = PoD (Dose predicted by PBPK model ÷ total UF; Total uncertainty factor =100X (10X intraspecies factor and 10X LOAEL to NOAEL extrapolation factor).
3 Steady state (21 day) food-only exposure estimates from Calendex (at 99.9$^{th}$ percentile).

### 6.3 Steady State Dietary (Food Service/Food Handling Establishments) Exposure and Risk Estimate

There are chlorpyrifos uses in food handling establishments (FHE) where food and food products are held, processed, prepared or served. These may include areas such as boxcars, shipping containers, and warehouses. FHE uses in restaurants, or similar service areas where food is prepared and served, may also be referred to as *food service establishment* (FSE) uses. There are no tolerances for the chlorpyrifos uses in FHEs except for the specific use of chlorpyrifos in FSEs as stated in the 40 CFR§180.342 (a) (3):

*A tolerance of 0.1 part per million is established for residues of chlorpyrifos, per se, in or on food commodities (other than those already covered by a higher tolerance as a result of use on growing crops) in food service establishments where food and food products are prepared and served, as a result of the application of chlorpyrifos in microencapsulated form.*

Typically, where there are established tolerances for FSE (or FHE) uses, anticipated residues for *all* foods would be included in the dietary assessment along with the residues on the foods with crop tolerances. The food only exposures in Section 6.2do not incorporate potential exposure from residues that may result on foods from FSE uses and, therefore, may underestimate actual exposures. A previous dietary risk assessment included a chronic analysis for FSE uses (D. Soderberg, D388166, 6/11/2011). This analysis was based on a BEAD estimate of < 2% of

establishments treated with chlorpyrifos and half the analytical limit of detection (½ LOD; 0.01 ppm) based on all nondetectable residues in a chlorpyrifos FHE study. That analysis resulted in a chronic dietary exposure of 0.009 µg/kg for children ages 1-2 years old (highest exposed population subgroup). HED has used this exposure value to compare to the ssPAD for children ages 1-2 years old. For the FSE uses alone, the children ages 1-2 years old steady state dietary (food only) exposures for chlorpyrifos are of concern, with an estimated risk of 530% of the ssPAD.

### 6.4 Dietary Drinking Water Risk Assessment

The total dietary exposure to chlorpyrifos is through both food and drinking water. EFED has provided a revised drinking water assessment (DWA) for chlorpyrifos (R. Bohaty, D432921, 04/14/2016) which includes the updated EDWCs for dietary risk assessment. A DWLOC approach is used to calculate the amount of exposure available in the total dietary 'risk cup' for chlorpyrifos in drinking water after accounting for chloropyrifos exposure from food. This DWLOC is then compared to the EDWC to determine if there is a risk of concern for drinking water exposures (See D. Drew, D424485, 12/29/2014 for details on the DWLOC approach and calculations). However, because the dietary risks from food alone are of concern (exceed the ssPAD), it is not possible to calculate a DWLOC; essentially the steady state DWLOC is '0' after accounting for food exposures.

Hypothetically, if there were no exposure to chlorpyrifos from food, and the entire dietary 'risk cup' was available for drinking water, the resulting steady state DWLOC for infants (the most highly exposed population subgroup for water) would be 0.014 ppb. An EDWC at or exceeding this concentration would be considered a risk of concern for exposures to chlorpyrifos in drinking water.

## 7.0 Residential (Non-Occupational) Exposure/Risk Characterization

Residential exposures to chlorpyrifos are currently expected from homeowner use. Formulations/use sites registered for homeowner use include a granular ant mound use and roach bait in child-resistant packaging. Additionally, chlorpyrifos is labeled for public health aerial and ground-based fogger ULV mosquito adulticide applications and for golf course turf applications. All residential exposures and risks were previously assessed in support of the 2014 HHRA (W. Britton, D424484, 12/29/2014). The previous assessment included evaluation of residential post-application risks from playing golf on chlorpyrifos-treated courses and from exposures which can occur following aerial and ground-based ULV mosquito adulticide usage. The potential for residential exposures from the roach bait product was determined to be negligible. Further, residential exposures from the ant mound use were also determined to be negligible since these products can only be applied professionally and direct exposure with treated ant mounds is not anticipated.

In addition to the assessment of residential exposure, the potential for post-application exposures to residential bystanders who live on, work in, or frequent areas adjacent to treated fields from spray drift and volatilization were also evaluated and presented in the 2014 HHRA.

The previously assessed residential post-application, residential bystander/volatilization, and non-occupational spray drift risk estimates have been updated to incorporate the approach applied for PBPK-derivation of PoDs for infants, children, and adults based on the exposures estimated from the indoor crack and crevice uses of chlorpyrifos during the time of the CCCEH cohort.

### 7.1 Residential Handler Exposure/Risk Estimates

HED uses the term "handlers" to describe those individuals who are involved in the pesticide application process. HED believes that there are distinct tasks related to applications and that exposures can vary depending on the specifics of each task. Residential handlers are addressed somewhat differently by HED 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 roach bait products can be applied by a homeowner in a residential setting but the application of roach bait products has not quantitatively assessed because these exposures are negligible. The roach bait product is designed such that the active ingredient is contained within a bait station which eliminates the potential for contact with the chlorpyrifos containing bait material. Therefore, updated residential handler risks are not required for these uses.

### 7.2 Residential Post-application Exposure/Risk Estimates

Residential post-application exposures are likely from 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 ant mound treatment was assessed qualitatively as addressed above because negligible exposures are anticipated.

All of the residential post-application exposure scenarios, data and assumptions, and algorithms used to assess exposures and risks from activities on golf course turf following chlorpyrifos application are the same as those used in the 2014 HHRA and ORE assessment. Additionally, this updated assessment makes use of the same chemical-specific turf transferable residue (TTR) data used previously to assess exposures and risks from golfing. Only the PoDs and LOCs have changed.

The residential post-application exposures and risks resulting from aerial and ground-based ULV mosquito adulticide applications have also been updated to reflect the updated PoDs and LOCs. However, the risks from the exposure scenarios have also been updated to reflect 1) the current default deposition fraction recommended for ground applied ULV mosquitocides (i.e., 8.7 percent of the application rate vs the previous 5 percent) and 2) several iterations of aerial applications modeled assuming differing winds speeds and release heights allowed by chlorpyrifos mosquitocide ULV labels. All other inputs and algorithms used for assessment of these exposure scenarios in 2014 remain the same, including the use of the chemical-specific TTR data. The AgDISP (v8.2.6) model input parameters, outputs, and the algorithms used to estimate residential post-application exposures following aerial and ground-based ULV

mosquitocide application can be found in Appendix A.

*Default deposition fraction for ground applied ULV mosquitocides*: Previously, an off-target deposition rate of 5 percent of the application rate was used by HED to evaluate ground-based ULV applications (i.e., 5 percent of the target application rate deposits on turf). This recommendation was based on data from Tietze *et al.,* and Moore *et al.* In a 2013 analysis (C. Peck, D407817, 3/28/2013), the Environmental Fate and Effects Division (EFED) reviewed eight published studies on ground ULV application in which deposition was measured. The studies varied in collection media (i.e., grass clippings and coupons), distance from application or spray head (ranging from 8 meters to 500 meters), and chemical measured (i.e., fenthion, malathion, naled, and permethrin). The analysis included the Moore *et al.,* and Tietze *et al.*, studies cited above. After considering the available data, HED has determined that an off-target deposition rate of 8.7 percent of the application rate may be used by HED to evaluate ground-based ULV applications (i.e., 8.7 percent of the target application rate deposits on turf). This value is the 90 percent upper confidence limit on the mean and is slightly higher than the mean values from all the data points observed in the studies (7.1%, n= 94). The adjusted application rate was then used to define TTR levels by scaling the available TTR data as appropriate.

*Aerial application wind speed, volume median diameter, and release height:* Previously, HED used the AgDISP (v8.2.6) model to assess deposition and air concentrations from aerial ULV applications assuming a 1 mph wind speed, volume median diameter is less than 60 µm (Dv 0.5 < 60 µm), and 300 foot release height. For this updated assessment, bounding risks have been estimated using the model based on a range of labeled application parameters. Lower spray height and lower wind speeds, and a greater Dv 0.5, results in the worst case potential exposures, or reduced potential for spray drift and, as a result, a greater deposition fraction and 1 hour average concentration. Therefore, estimated dermal and inhalation risks would be greater under these application conditions. The reverse is true for the best-case modeling scenario.

- Worst-case - 1 mph wind speed, Dv 0.5 = 60 µm, and 75 foot release height; and
- Best-case - 10 mph wind speed, Dv 0.5 = 40 µm, and 300 foot release height.

The following inputs were used for AgDISP (v8.26) modeling of chlorpyrifos ULV aerial applications.

**Table 7.2.1. AGDISP Inputs (v8.26): Chlorpyrifos Mosquitocide ULV Aerial Application.**

| Input Parameters | Inputs to include in the AgDISP model | Notes/Comments |
|---|---|---|
| Application Method | Aerial | Default |
| Aircraft | Air Tractor AT-401 | Default |
| Release Height | 75, 300 Feet minimum release | Label allows a release height ranging from 75 to 300 feet. |
| Spray Lines | 20 Reps | Default |
| Application Technique | Liquid | Default |
| Application Technique *Nozzles* | 3; Extent 76.3%; Spacing 18.7 ft | Default |
| Application Technique *Drop Size Distribution* | User defined Parametric; $D_{V0.5}$: 40, 60 µm; and relative span: 1.4. | A $D_{v0.5}$ value of < 60 µm is allowable on the label. A $D_{v0.5}$ value of < 40 µm was modeled to estimate a lower droplet size |

| Table 7.2.1. AGDISP Inputs (v8.26): Chlorpyrifos Mosquitocide ULV Aerial Application. | | |
|---|---|---|
| **Input Parameters** | **Inputs to include in the AgDISP model** | **Notes/Comments** |
| | no conversion to Malvern<br>Drop Size Distribution | as is typically used for ULV aerial application. |
| Swath Width | 500 feet | Default |
| Swath Displacement | Worst case application parameters: -130 feet<br><br>Best case application parameters: 3,729 feet | The modeled spray deposition shows the peak deposition to be at a distance other than 0 feet. Therefore, the swath displacement w changed to the horizontal distance from the y axis where the peak deposition occurred and then the air concentration value was selected at this distance. |
| Meteorology | Wind type: single height<br>Wind speed: 1, 10 mph<br>Wind direction: -90 deg<br>Temperature: 85 F°<br>Relative humidity: 50% | No wind speed was identified on the label. The wind speeds of 1 and 10 mph were modeled to represent a reasonable range of wind speeds typical of ULV aerial applications. |
| Spray Material | Name: Oil<br>Spray Material Evaporates: Yes<br>Spray volume rate: 1.5 (gal/A)<br>Active Fraction: 0.1936<br>Nonvol Fraction: 1 | Spray material criteria as defined by the product label. |
| Atmospheric Stability | Overcast | Default |
| Surface | Upslope angle: 0 deg<br>Sideslope angle: 0 deg<br>Canopy: None | Default |
| Transport | Distance: 0 feet | Default |
| Advanced | Default Swatch offset: 0 Swath<br><br>Specific Gravity carrier: Oil<br>Specific Gravity active and additive= 0.929<br>Evaporation Rate: 84.76 | Inputs based on criteria as defined by the product label. |

Summary of Residential Post-application Non-Cancer Exposure and Risk Estimates

A summary of risk estimates is presented in Tables 7.2.2 through 7.2.8 below.

All residential post-application exposure scenarios assessed for playing golf on chlorpyrifos-treated courses, including all relevant populations and in consideration of all TTR data state sites, result in risks of concern (i.e., MOEs are < 100). Further, all residential post-application exposure scenarios assessed following aerial and ground ULV mosquitocide application result in risks of concern. All risk estimates are provided in Appendix B.

| Table 7.2.2. Residential Post-application Non-cancer Exposure and Risk Estimates from Playing Golf on Chlorpyrifos-Treated Courses. | | | | | | |
|---|---|---|---|---|---|---|
| **Lifestage** | **Post-application Exposure Scenario** | | **Application Rate[1]** | **State (TTR Data)** | **Dose (mg/kg/day)[2]** | **MOEs[3]** |
| | **Use Site** | **Route of Exposure** | | | | |
| Adult | Golf Course | Dermal | 1.0 | CA | 0.010 | 0.13 |

**Table 7.2.2. Residential Post-application Non-cancer Exposure and Risk Estimates from Playing Golf on Chlorpyrifos-Treated Courses.**

| Lifestage | Post-application Exposure Scenario | | Application Rate[1] | State (TTR Data) | Dose (mg/kg/day)[2] | MOEs[3] |
|---|---|---|---|---|---|---|
| | Use Site | Route of Exposure | | | | |
| (Females) | Turf | | (Emulsifiable Concentrate) | IN | 0.0069 | 0.19 |
| | | | | MS | 0.012 | 0.11 |
| | | | | Mean | 0.0095 | 0.14 |
| Youths 11 to < 16 years old | | | | CA | 0.010 | 0.14 |
| | | | | IN | 0.0070 | 0.20 |
| | | | | MS | 0.012 | 0.12 |
| | | | | Mean | 0.0096 | 0.15 |
| Children 6 to < 11 years old | | | | CA | 0.012 | 0.19 |
| | | | | IN | 0.0082 | 0.27 |
| | | | | MS | 0.014 | 0.16 |
| | | | | Mean | 0.011 | 0.20 |
| Adult (Females) | | | 1.0 (Granular) | CA | 0.0088 | 0.15 |
| Youths 11 to < 16 years old | | | | | 0.0088 | 0.16 |
| Children 6 to < 11 years old | | | | | 0.010 | 0.21 |

1 Based on the maximum application rates registered for golf course turf use.
2 Dose (mg/kg/day) equations for golfing are provided in Appendix B of the 2014 HHRA. For dose estimation from exposures to golfing on treated turf TTR data was used. Doses have been presented for all State sites, including the mean of all State sites.
3 MOE = PoD (mg/kg/day) ÷ Dose (mg/kg/day). See Table 5.3.3.3 for PODs.

**Table 7.2.3. Residential Post-application Inhalation Steady State Exposure Estimates from Chlorpyrifos ULV Aerial Mosquitocide Application - AgDISP Model.**

| Application Parameters | Population | Air Concentration Estimate ($mg/m^3$)[1] | MOE[2] |
|---|---|---|---|
| 1 mph Wind Speed<br>Dv 0.5 = 60 µm<br>75 Foot Release Height | Adults | 0.0047 | **1.1** |
| | Children 1 to <2 years old | | **0.35** |
| 10 mph Wind Speed<br>Dv 0.5 = 40 µm<br>300 Foot Release Height | Adults | 0.00070 | **7.3** |
| | Children 1 to <2 years old | | **2.4** |

1 Air concentration estimate modeled using AGDISP v8.2.6 at breathing height of adults and children.
2 MOE = PoD ($mg/m^3$) ÷ Dose ($mg/m^3$). See Table 5.3.3.3 for PODs.

**Table 7.2.4. Residential Post-application Inhalation Steady State Exposure Estimates from Chlorpyrifos ULV Ground Mosquitocide Application - WMB Model.**

| Population | Air Concentration Estimate ($mg/m^3$)[1] | MOE[2] |
|---|---|---|
| Adults | 0.0013 | **0.66** |
| Children 1 to <2 years old | | **0.21** |

1 Air concentration estimate modeled using the well mixed box model. The inputs and algorithms used are presented in Appendix C of the 2014 HHRA.
2 MOE = PoD ($mg/m^3$) ÷ Dose ($mg/m^3$). See Table 5.3.3.3 for PODs.

**Table 7.2.5. Residential Post-application Dermal Steady State Exposure Estimates Resulting from Chlorpyrifos Aerial ULV Mosquitocide Application.**

| Application Parameters | Lifestage | Application Rate (lb ai/A) | AgDISP Deposition Fraction[1] | Adjusted TTR[2] (µg/cm²) | Dermal Dose[3] (mg/kg/day) | MOE[4] |
|---|---|---|---|---|---|---|
| 1 mph Wind Speed<br>Dv 0.5 = 60 µm<br>75 Foot Release Height | Adults | 0.010 | 1.0 | 0.00038 | 0.0015 | **2** |
| | Children 1 to < 2 Years Old | | | | 0.0026 | **6** |
| 10 mph Wind Speed<br>Dv 0.5 = 40 µm<br>300 Foot Release Height | Adults | 0.010 | 0.086 | 0.000033 | 0.00013 | **27** |
| | Children 1 to < 2 Years Old | | | | 0.00022 | **68** |

1 Aerial fraction of mosquitocide application rate deposited on turf as determined using AgDISP model v8.2.6.
2 $TTR_t$ (µg/cm²) = [(Day 0 Residue from MS TTR study (µg/cm²) x Application Rate (0.010 lb ai/A)) / Application Rate of MS TTR Study (3.83 lb ai/A))] * AgDISP Deposition Fraction
3 Dermal Dose (mg/kg/day) = [ ($TTR_t$ (µg/cm²) * CF1 (0.001 mg/µg) * Transfer Coefficient (180,000 cm²/hr, adults; 49,000 cm²/hr, children) * ET (1.5 hrs)) ] ÷ BW (kg)
4 MOE = PoD (mg/kg/day) ÷ Dose (mg/kg/day). See Table 5.3.3.3 for PODs.

**Table 7.2.6. Residential Post-application Dermal Steady State Exposure Estimates Resulting from Chlorpyrifos ULV Ground Mosquitocide Application.**

| Lifestage | Application Rate (lb ai/A) | Deposition Fraction[1] | Adjusted TTR[2] (µg/cm²) | Dermal Dose[3] (mg/kg/day) | MOE[4] |
|---|---|---|---|---|---|
| Adults | 0.010 | 1.0 | 0.00038 | 0.0015 | **26** |
| Children 1 to < 2 Years Old | | | | 0.0026 | **67** |

1. Ground fraction of mosquitocide application rate deposited on turf as determined using eight published studies on ground ULV application in which deposition was measured.
2. $TTR_t$ (µg/cm²) = [(Day 0 Residue from MS TTR study (µg/cm²) x Application Rate (0.010 lb ai/A)) / Application Rate of MS TTR Study (3.83 lb ai/A))] * AgDISP Deposition Fraction
3. Dermal Dose (mg/kg/day) = [ ($TTR_t$ (µg/cm²) * CF1 (0.001 mg/µg) * Transfer Coefficient (cm²/hr - 180,000, adults; 49,000, children) * ET (1.5 hrs)) ] ÷ BW (kg)
4. MOE = PoD (mg/kg/day) ÷ Dose (mg/kg/day). See Table 5.3.3.3 for PODs.

**Table 7.2.7. Residential Post-application Steady State Incidental Oral Exposure Estimates Resulting from Chlorpyrifos ULV Aerial Mosquitocide Application.**

| Application Parameters | Lifestage | Application Rate (mg ai) | Dermal Exposure (mg/day)[1] | Incidental Oral Dose (mg/kg/day)[2] | MOE[3] |
|---|---|---|---|---|---|
| 1 mph Wind Speed<br>Dv 0.5 = 60 µm<br>75 Foot Release Height | Children 1 to < 2 Years Old | 0.010 | 0.028 | $5.2 \times 10^{-5}$ | **3** |
| 10 mph Wind Speed | | | 0.0022 | $4.5 \times 10^{-6}$ | **38** |

| | | | | | |
|---|---|---|---|---|---|
| Dv 0.5 = 40 µm<br><br>300 Foot Release Height | | | | | |

1 Dermal exposure (mg/day) as calculated for children's aerial based ULV applications using the algorithms described in Table 6.2.4 above, and as described in Appendix C of the 2014 HHRA.
2 Incidental Oral Dose estimated using the algorithms as described below in Appendix C of the 2014 HHRA.
3 MOE = PoD (mg/kg/day) ÷ Dose (mg/kg/day). See Table 5.3.3.3 for PODs.

**Table 7.2.8. Residential Post-application Steady State Incidental Oral Exposure Estimates Resulting from Chlorpyrifos ULV Ground Mosquitocide Application.**

| Lifestage | Application Rate (mg ai) | Dermal Exposure (mg/day)[1] | Incidental Oral Dose (mg/kg/day)[2] | MOE[3] |
|---|---|---|---|---|
| Children<br>1 to < 2 Years Old | 0.010 | 0.0024 | $4.5x10^{-6}$ | 37 |

1 Dermal exposure (mg/day) as calculated for children's ground based ULV applications using the algorithms described in Table 6.2.5 above, and as described below in Appendix C of the 2014 HHRA.
2 Incidental Oral Dose estimated using the algorithms as described in Appendix C of the 2014 HHRA.
3 MOE = PoD (mg/kg/day) ÷ Dose (mg/kg/day). See Table 5.3.3.3 for PODs.

## 7.3 Residential Risk Estimates for Use in Aggregate Assessment

All residential risks assessed with the updated PBPK-derived PODs are of concern (i.e., all MOEs are < the LOC of 100). Therefore, quantitatively aggregating residential exposures with food and drinking water exposures would also result in risks of concern.

## 8.0 Non-Occupational Spray Drift Exposure and Risk Estimates

Spray drift is a potential source of exposure to those nearby pesticide applications. This is particularly the case with aerial application, but, to a lesser extent, spray drift can also be a potential source of exposure from the ground application methods (e.g., groundboom and airblast) employed for chlorpyrifos. Sprays that are released and do not deposit in the application area end up off-target and can lead to exposures to those it may directly contact. They can also deposit on surfaces where contact with residues can eventually lead to indirect exposures (*e.g.*, children playing on lawns where residues have deposited next to treated fields). The potential risk estimates from these residues can be calculated using drift modeling coupled with methods employed for residential risk assessments for turf products.

In the 2011 occupational and residential exposure assessment, the potential risks to bystanders from spray drift and exposure from volatilization were identified as possible concerns. Spray drift is the movement of aerosols and volatile components away from the treated area during the application process. The potential risks from spray drift and the impact of potential risk reduction measures were assessed in July 2012 (J. Dawson *et al.*, D399483, 07/13/2012). This evaluation supplemented the 2011 assessment where limited monitoring data indicate risks to bystanders. To increase protection for children and other bystanders, chlorpyrifos technical registrants voluntarily agreed to lower application rates and to other spray drift mitigation measures (R. Keigwin, 2012). As of December 2012, spray drift mitigation measures and use restrictions appear on all chlorpyrifos agricultural product labels. For the 2014 HHRA, spray drift risks were updated due to the use of the PBPK-PD model which impacted the PoDs, and

thus spray drift risk estimates. This assessment updates chlorpyrifos risks once more to incorporate the approach applied for PBPK-derivation of PoDs for infants, children, and adults based on the exposures estimated from the indoor crack and crevice uses of chlorpyrifos during the time of the CCCEH cohort.

With a dermal and incidental oral LOC of 100, all non-occupational spray drift risk estimates are of concern at the field edge with the use of certain application rates, nozzle droplet sizes, and application methods. Buffer distances > 300 feet are needed for MOEs to be not of concern. The estimated buffer distances are in excess of those agreed to by the technical registrants in July 2012. All drift risk estimates are presented in Appendix C.

## 9.0 Non-Occupational Bystander Post-Application Inhalation Exposure and Risk Estimates

In January 2013, a preliminary assessment of the potential risks from volatilization was conducted (R. Bohaty *et al.,* D399484 and D400781, 01/31/2013). The assessment evaluated the potential risks to bystanders, or those who live and/or work in proximity to treated fields, from inhalation exposure to vapor phase chlorpyrifos and chlorpyrifos-oxon emitted from fields following application of chlorpyrifos. The results of the January 2013 assessment indicated that offsite concentrations of chlorpyrifos and chlorpyrifos-oxon may exceed the target concentration based on the toxicological endpoints used at that time (J. Hotchkiss *et al.,* EPA MRID 48139303).

In June 2014, a re-evaluation of the 2013 preliminary volatilization assessment was conducted since the Registrant had conducted and submitted two, high quality nose-only vapor phase AChE inhibition inhalation studies for both chlorpyrifos and chlorpyrifos-oxon (W. Irwin, D411959, 06/25/2014) to address the uncertainty surrounding exposure to aerosol versus vapor phase chlorpyrifos. In the vapor studies, female rats were administered a saturated vapor, meaning that the test subjects received the highest possible concentration of chlorpyrifos or chlorpyrifos-oxon which can saturate the air in a closed system. At these saturated concentrations, no statistically significant inhibition of AChE activity was measured in RBC, plasma, lung, or brain at any time after the six-hour exposure period in either study. Under actual field conditions, indications are that exposures to vapor phase chlorpyrifos and its oxon would be much lower as discussed in the January 2013 preliminary volatilization assessment. Since the studies demonstrated that no toxicity occurred even at the saturation concentration, the agency concluded that there was no risk potential, as risk is a function of both exposure and hazard.

However, in the current risk assessment for chlorpyrifos, the PoDs for risk assessment have been chosen to be protective of potential neurological effects below levels where AChE inhibition could occur. For that reason, a quantitative bystander/volatilization assessment has been included in this update. This assessment is an update to the 2013 assessment and has been updated to reflect air monitoring data collected since 2006, and the updated PoDs for chlorpyrifos.

There are six available chlorpyrifos air monitoring studies that were conducted since 2006 (brief study summaries available in W. Britton, D388165, 06/27/2011). These include:

- One application site study conducted in North Central and Yakima Valley, OR by the University of Washington Department of Environmental and Occupational Health Sciences, and
- Five ambient air studies
    - one conducted in North Central and Yakima Valley, by the University of Washington Department of Environmental and Occupational Health Sciences;
    - two conducted by Pesticide Action Network North America (PANNA) in Washington and Minnesota; and
    - two conducted by CalDPR.

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

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

The EPA has assessed residential bystander exposure to chlorpyrifos based on the available ambient and application site air monitoring data (Tables 9.1 and 9.2). The chlorpyrifos bystander volatilization inhalation exposure assessment includes acute and steady state exposure scenarios. The acute scenario compares the maximum air concentration detected in the monitoring studies to the acute PoD. The steady state scenario compares the arithmetic mean chlorpyrifos air concentration from several monitoring studies to the steady state PoD.

The EPA has assessed residential bystander exposure from field volatilization of applied chlorpyrifos based on available *ambient* (five studies/11 locations) and *application site* (one study/2 locations) air monitoring data. For adults, of the 11 acute *ambient* air concentrations assessed, six resulted in risk estimates that are of concern (i.e., MOEs < 100). Only one steady state *ambient* air concentration resulted in a risk estimate not of concern (i.e., MOEs > 100). For the *application site* air concentrations assessed, all resulted in risk estimates of concern (i.e., MOEs < 100). For children 1 to <2 years old, of the 11 acute *ambient* air concentrations assessed, all resulted in risk estimates that are of concern (i.e., MOEs < 100). Only four steady state *ambient* air concentration resulted in a risk estimate not of concern (i.e., MOEs > 100). For the *application site* air concentrations assessed, all resulted in risk estimates of concern (i.e.,

MOEs < 100). All bystander risk estimates are presented in Appendix D.

**Table 9.1. Chlorpyrifos Preliminary Volatilization Risk Analysis for Residential Adult Bystanders.**

| Study, Year | Sampler/ Site Location | Maximum Air Concentration (ng/m$^3$) | Arithmetic Mean Air Concentration (ng/m$^3$) | Acute MOEs[1] (LOC = 100) | Steady State MOEs[2] (LOC = 100) |
|---|---|---|---|---|---|
| **Application Site Data** | | | | | |
| WA DOH, 2008 | North Central District Perimeter Site | 1145 | 153 | **3.5** | **1.4** |
| | Yakima Valley Perimeter Site | 1002 | 294 | **4** | **0.71** |
| **Ambient Air Data** | | | | | |
| WA DOH, 2008 | North Central District Ambient | 21 | 7 | 190 | **31** |
| | North Central District Receptor | 606.8 | 33 | **6.6** | **6.4** |
| | Yakima Valley Ambient | 30 | 9 | 130 | **23** |
| | Yakima Valley Receptor | 243 | 30 | **16** | **6.9** |
| Parlier, CA (CalDPR) 2009 | | 150 | 96 | **27** | **2.2** |
| Cowiche PANNA 2006 | | 462 | 155 | **8.7** | **1.4** |
| PANNA MN Drift Study (2006-2009) | Browerville Site B | 15 | 2.7 | 270 | **79** |
| | Perham Site C | 47 | 1.9 | **85** | 110 |
| CDPR 2014 Air Monitoring Network | Salinas, CA | 14.1 | 5.4 | 280 | **39** |
| | Shafter, CA | 337.9 | 92.1 | **12** | **2.3** |
| | Ripon, CA | 14.1 | 14.1 | 280 | **15** |

1 Acute MOE = Acute PoD (4,000 ng/m$^3$) / Study maximum air concentration (ng/m$^3$).
2 Steady State MOE = Steady State PoD (210 ng/m$^3$) / Study arithmetic mean air concentration (ng/m$^3$).

**Table 9.2. Chlorpyrifos Preliminary Volatilization Risk Analysis for Residential Children (1 to <2 Years Old) Bystanders.**

| Study, Year | Sampler/ Site Location | Maximum Air Concentration (ng/m$^3$) | Arithmetic Mean Air Concentration (ng/m$^3$) | Acute MOEs[1] (LOC = 100) | Steady State MOEs[2] (LOC = 100) |
|---|---|---|---|---|---|
| **Application Site Data** | | | | | |
| WA DOH, 2008 | North Central District Perimeter Site | 1145 | 153 | **1.1** | **4.4** |
| | Yakima Valley Perimeter Site | 1002 | 294 | **1.3** | **2.3** |
| **Ambient Air Data** | | | | | |
| WA DOH, 2008 | North Central District Ambient | 21 | 7 | **62** | 100 |
| | North Central District Receptor | 606.8 | 33 | **2.1** | **21** |
| | Yakima Valley Ambient | 30 | 9 | **43** | **73** |
| | Yakima Valley Receptor | 243 | 30 | **5.3** | **22** |

**Table 9.2. Chlorpyrifos Preliminary Volatilization Risk Analysis for Residential Children (1 to <2 Years Old) Bystanders.**

| Study, Year | Sampler/ Site Location | Maximum Air Concentration ($ng/m^3$) | Arithmetic Mean Air Concentration ($ng/m^3$) | Acute MOEs[1] (LOC = 100) | Steady State MOEs[2] (LOC = 100) |
|---|---|---|---|---|---|
| Parlier, CA (CalDPR) 2009 | | 150 | 96 | **8.7** | **7.1** |
| Cowiche PANNA 2006 | | 462 | 155 | **2.8** | **4.4** |
| PANNA MN Drift Study (2006-2009) | Browerville Site B | 15 | 2.7 | **87** | 260 |
| | Perham Site C | 47 | 1.9 | **28** | 350 |
| CDPR 2014 Air Monitoring Network | Salinas, CA | 14.1 | 5.4 | **92** | 130 |
| | Shafter, CA | 337.9 | 92.1 | **3.8** | **7.4** |
| | Ripon, CA | 14.1 | 14.1 | **92** | **48** |

1 Acute MOE = Acute PoD (1,300 $ng/m^3$) / Study maximum air concentration ($ng/m^3$).
2 Steady State MOE = Steady State PoD (680 $ng/m^3$) / Study arithmetic mean air concentration ($ng/m^3$).

*Characterization of Bystander Risk Assessment/Uncertainties*

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

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

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

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

- As part of the December 2009 SAP, the agency presented their analysis of several models that could be used as screening tools to predict the air concentration and volatilization flux based on intrinsic properties and transport behaviors of pesticides. These models would allow the agency to better represent the potential volatilization of semi-volatile

pesticides across various regions of the country and thus would provide refinement to this assessment over using straight air monitoring data. The SAP provided a number of comments regarding the agency's model analysis, including the recommendation to evaluate some additional models. The agency is currently in the process of evaluating the SAP's comments. As appropriate, the agency will revise the modeling approach presented to the SAP for determining the rate of volatilization (flux) for semi-volatile pesticides and for estimating air concentrations of applied pesticides in the atmosphere under varying environmental conditions. After any policies or procedures are put into place, the agency may revisit the residential bystander exposure and risk assessment.

## 10.0 Aggregate Exposure/Risk Characterization

In accordance with the FQPA, HED must consider and aggregate (add) 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 steady state aggregate assessment includes food, drinking water, and residential exposures.

For chlorpyrifos aggregate assessment, a DWLOC approach is used to calculate the amount of exposure available in the total 'risk cup' for chlorpyrifos in drinking water after accounting for any chloropyrifos exposures from food and residential uses. This DWLOC is then compared to the EDWC to determine if there is an aggregate risk of concern. However, because the dietary risks from food exposure alone and from residential exposure alone are of concern, it is not possible to calculate a DWLOC; essentially, the steady state aggregate DWLOC is '0' after accounting for food and residential exposures.

[See the December 2014 chlorpyrifos HHRA for details of the DWLOC approach and calculations. See the April 2016 DWA for the EDWCs.]

## 11.0 Occupational Exposure and Risk Estimates

HED had previously conducted both steady state occupational handler and post-application exposure analyses for chlorpyrifos (W. Britton, D424484, 12/29/2014). However, occupational exposures and risks have been updated to incorporate the approach applied for PBPK-derivation of PoDs for infants, children, and adults based on the exposures estimated from the indoor crack and crevice uses of chlorpyrifos during the time of the CCCEH cohort. The scenarios, assumptions, and exposure inputs have not changed since the previous assessment; the assessment below estimates occupational handler exposures using the updated PBPK-derived steady state PoDs. Details on the exposure inputs, scenarios, and assumptions can be found in the 2014 ORE assessment (W. Britton, D424484, 12/29/2014).

It is agency policy to use the best available data to assess exposure. The same chemical-specific dislodgeable foliar residue (DFR) studies were used for the 2014 assessment of occupational post-application exposure to chlorpyrifos have been used for this update, including: emulsifiable concentrate formulations on sugarbeets, pecans, citrus, sweet corn, cotton, and turf; wettable powder formulations on almonds, apples, pecans, cauliflower, tomato and turf; granular

formulations on sweet corn and turf; a total release aerosol formulation on ornamentals; and a microencapsulated liquid formulation on ornamentals.

Several sources of generic data were used in this assessment as surrogate data including: Pesticide Handlers Exposure Database Version 1.1 (PHED 1.1); the Agricultural Handler Exposure Task Force (AHETF) database; the Outdoor Residential Exposure Task Force (ORETF) database; the Agricultural Reentry Task Force (ARTF) database; ExpoSAC Policy 14 [Standard Operating Procedures (SOPs) for Seed Treatment]; HED's 2012 Residential SOPs for Residential Pesticide Exposure Assessment: Lawns/Turf, Outdoor Fogging/Misting Systems, registrant-submitted exposure monitoring studies MRIDs 44180401, 44301301, 44793301, 44829601, 42974501, 43062701, 44748101, 44748102, 46722701, and 46722702, and published literature studies. Some of these data are proprietary, and subject to the data protection provisions of the *Federal Insecticide, Fungicide, and Rodenticide Act (*FIFRA).

In the 2011 HHRA (D. Drew *et al.,* D388070, 06/30/2011), additional studies were recommended to address uncertainties regarding the formation of chlorpyrifos oxon and its decay following applications in greenhouses. To date, no additional data have been submitted.

### 11.1 Steady State Occupational Handler Risk

The term handlers is used to describe those individuals who are involved in the pesticide application process. There are distinct job functions or tasks related to applications and exposures can vary depending on the specifics of each task. Job requirements (amount of a chemical used in each application), the kinds of equipment used, the target being treated, and the level of protection used by a handler can cause exposure levels to differ in a manner specific to each application event. Based on the anticipated use patterns and current labeling, types of equipment and techniques that can potentially be used, occupational handler exposure is expected from chlorpyrifos use. For purpose of occupational handler assessment, the parent chlorpyrifos is the relevant compound.

Current labels generally require that handlers use normal work clothing (i.e., long sleeved shirt and pants, shoes and socks) and coveralls, chemical resistant gloves, and dust/mist respirators. Also, some products are marketed in engineering controls such as water soluble packets. In order to determine what level of personal protection is required to alleviate risk concerns and to ascertain if label modifications are needed, steady state exposure and risk estimates were updated for occupational handlers of chlorpyrifos for a variety of scenarios at differing levels of personal protection including engineering controls.

The occupational handler scenarios, assumptions, and exposure inputs have not changed since the previous assessment.

<u>Summary of Occupational Handler Non-Cancer Exposures and Risk Estimates</u>
Using the updated PBPK-derived steady state PODs and uncertainty factors (dermal and inhalation LOC = 100), all agricultural occupational handler scenarios, all primary seed treatment handler scenarios, and all secondary seed treatment (planter) scenarios are of concern with label-specified and maximum levels of personal protective equipment (PPE) or engineering

controls (MOEs < 100). Detailed result tables are provided in Appendix E.

## 11.2 Steady State Occupational Post-Application Risk Estimates

HED uses the term, post-application, to describe exposures that occur when individuals are present in an environment that has been previously treated with a pesticide (also referred to as reentry exposure). Such exposures may occur when workers enter previously treated areas to perform job functions, including activities related to crop production, such as scouting for pests or harvesting. Post-application exposure levels vary over time and depend on such things as the type of activity, the nature of the crop or target that was treated, the type of pesticide application, and the chemical's degradation properties. In addition, the timing of pesticide applications, relative to harvest activities, can greatly reduce the potential for post-application exposure. Chlorpyrifos parent compound is the residue of concern for occupational post-application dermal exposures; however, it may be possible that the formation of the oxon is greater and its deactivation slower in greenhouses when compared to the outdoor environment and that an assessment may be needed for exposure to the oxon in greenhouse settings.

### 11.2.1 Occupational Post-application Inhalation Exposure/Risk Estimates

There are multiple potential sources of post-application inhalation exposure to individuals performing post-application activities in previously treated fields. These potential sources include volatilization of pesticides and resuspension of dusts and/or particulates that contain pesticides. Previously, a quantitative post-application inhalation risk assessment was not conducted for chlorpyrifos or chlorpyrifos oxon due to the lack of toxicity seen in the available nose-only vapor phase AChE inhibition inhalation studies (W. Britton, D424484, 12/29/2014). The studies did not demonstrate inhalation toxicity, or inhibition of AChE activity measured in RBC, plasma, the lungs, and the brain following exposure to chlorpyrifos or chlorpyrifos oxon vapor, even at the saturation concentration. However, since the previous assessment, the PODs have been updated to reflect the PBPK-derived steady state PoD based on a TWA of blood concentrations corresponding to levels likely to have occurred in the CCCEH cohort, as discussed in Section 5.3.3. Therefore, the agency will be assessing occupational post-application inhalation from the registered uses of chlorpyrifos.

The agency has sought expert advice and input on issues related to volatilization of pesticides from its Federal Insecticide, Fungicide, and Rodenticide Act Scientific Advisory Panel (SAP) in December 2009, and received the SAP's final report on March 2, 2010 (https://www.regulations.gov/document?D=EPA-HQ-OPP-2009-0687-0037). The agency has evaluated the SAP report and has developed a Volatilization Screening Tool and a subsequent Volatilization Screening Analysis (https://www.regulations.gov/document?D=EPA-HQ-OPP-2014-0219-0001). During Registration Review, the agency will utilize this analysis, and take into consideration the risks identified from the residential bystander assessment, to determine if data (i.e., flux studies) or further analysis is required for chlorpyrifos.

In addition, the agency is continuing to evaluate the available post-application inhalation exposure data generated by the Agricultural Reentry Task Force. Given these two efforts, the agency will continue to identify the need for and, subsequently, the way to incorporate

occupational post-application inhalation exposure into the agency's risk assessments.

The Worker Protection Standard for Agricultural Pesticides contains requirements for protecting workers from inhalation exposures during and after greenhouse applications through the use of ventilation requirements.[40 CFR 170.110, (3) (Restrictions associated with pesticide applications)].

### 11.2.2 Occupational Post-application Dermal Exposure/Risk Estimates

Occupational post-application assessments were previously performed for: 1) exposures to the parent compound chlorpyrifos in outdoor environments (uses other than greenhouse), 2) exposures to the parent chlorpyrifos (only) in greenhouses and 3) exposures to both the parent and the oxon metabolite in greenhouses; and incorporated: 1) a PBPK modeled dermal PoD specific for occupational assessment 2) the updated master use summary document, 3) the updated adult (female) default body weight, and 4) the changes relating to agricultural transfer coefficients (TC) as described in the *Science Advisory Council for Exposure (ExpoSAC) Policy 3 – Revised March 2013*[17] (W. Britton, D424484, 12/29/2014).

However, the steady state PODs and uncertainty factors have changed since the previous assessment. Therefore, the occupational post-application exposure assessment has been revised. The scenarios, assumptions, and exposure inputs have not changed since the previous assessment; the assessment below estimates occupational post-application dermal exposures using the updated PBPK-derived steady state PODs. Details on the exposure inputs, scenarios, and assumptions can be found in W. Britton, D424484, 12/29/2014. Detailed result tables are provided in Appendix F.

Summary of Occupational Post-application Non-Cancer Exposures and Risk Estimates
263 total occupational post-application scenarios were evaluated. The restricted entry intervals (REIs) on the registered chlorpyrifos labels range from 24 hours to 5 days. All scenarios were of concern on Day 0 with a dermal LOC of 100. On average, scenarios were not of concern $\geq$ 18 days after treatment.

[17] http://www.epa.gov/opp00001/science/exposac-policy-3-march2013.pdf

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