



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

OFFICE OF CHEMICAL SAFETY  
AND POLLUTION PREVENTION

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Re: Chlorpyrifos petition dated September 12, 2007

Dear Mr. Colangelo and Dr. Reeves:

This letter constitutes the U.S. Environmental Protection Agency's (EPA or Agency) partial response to the petition dated September 12, 2007 (Petition), submitted jointly by the Natural Resources Defense Council (NRDC) and Pesticide Action Network North America (PANNA). The petition specifically requested that EPA revoke all tolerances and cancel all registrations for the insecticide chlorpyrifos.<sup>1</sup> The petition provided that it was filed pursuant to 21 U.S.C. section 346a(d) (section 408(d)) of the Federal Food Drug and Cosmetic Act (FFDCA)).

In the petition, NRDC and PANNA claimed that in 2006, when the Agency finalized its Organophosphorus (OP) Cumulative Risk Assessment – 2006 Update<sup>2</sup> (CRA) for all organophosphates, which included chlorpyrifos, and reaffirmed the 2001 chlorpyrifos Interim Reregistration Eligibility Decision (IRED), it failed to properly consider data that demonstrated adverse effects from chlorpyrifos exposure. More specifically, petitioners made the following ten claims regarding the Agency's cumulative assessment for all organophosphates and the chlorpyrifos IRED:

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<sup>1</sup> Petition of Natural Resources Defense Council and Pesticide Action Network North America to Revoke All Tolerances and Cancel All Registrations for the Pesticide Chlorpyrifos (September 12, 2007) at 1. (hereinafter Petition) Available at <http://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPP-2007-1005-0005>.

<sup>2</sup> U.S. Environmental Protection Agency (EPA) (2006). Organophosphorus Cumulative Risk Assessment – 2006 Update. Available at [http://www.epa.gov/opp00001/cumulative/2006-op/op\\_cra\\_main.pdf](http://www.epa.gov/opp00001/cumulative/2006-op/op_cra_main.pdf).

1. EPA ignored genetic evidence of vulnerable populations
2. EPA needlessly delayed a decision regarding endocrine disrupting effects
3. EPA ignored data regarding cancer risks
4. EPA's CRA misrepresented risks, failed to apply FQPA 10X safety factor<sup>3</sup>
5. EPA over-relied on registrant data
6. EPA failed to properly address the exporting hazard from chlorpyrifos
7. EPA failed to quantitatively incorporate data demonstrating long-lasting effects from early life exposure to chlorpyrifos in children
8. EPA disregarded data demonstrating that there is no evidence of a safe level of exposure during pre-birth and early life stages
9. EPA failed to cite or quantitatively incorporate studies and clinical reports suggesting potential adverse effects below 10% cholinesterase inhibition
10. EPA failed to incorporate inhalation routes of exposure

This partial Agency response to the petition addresses the first six claims listed above: genetic evidence of vulnerable populations; endocrine disrupting effects; cancer risks; CRA misrepresents risks, fails to apply FQPA 10X safety factor; over-reliance on registrant data; and exporting hazard. EPA's response to three of petitioners' remaining four claims -- that EPA failed to quantitatively incorporate data exhibiting long-lasting effects from early life exposure to chlorpyrifos in children; that EPA disregarded data demonstrating that there is no evidence of a safe level of exposure during pre-birth and early life stages; and that EPA failed to cite or quantitatively incorporate studies and clinical reports suggesting potential adverse effects below 10% cholinesterase inhibition -- involve highly complex assessments, using precedent setting risk assessment methodologies. For this reason, consistent with EPA's external scientific peer review policy, the Agency sought advice on these issues from the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) Scientific Advisory Panel (SAP) at a meeting that occurred April 10-13, 2012. As to the petitioners' fourth remaining claim -- that EPA failed to incorporate inhalation routes of exposure -- EPA is today releasing its "Evaluation of the Potential Risks From Spray Drift and the Impacts of Potential Risk Reduction Measures"<sup>4</sup> that further refines its analysis of spray drift from chlorpyrifos that was presented in the preliminary human health risk assessment (HHRA) released in July 2011. In connection with this spray drift assessment, the chlorpyrifos registrants have agreed to implement label mitigation (in the form of rate reductions and spray drift buffers) that will reduce risks to bystanders from spray drift. EPA's spray drift assessment and the associated mitigation action are not intended to provide a complete response to petitioners' fourth claim since this mitigation action does not take into account potential exposures from volatilization following chlorpyrifos applications. That work is ongoing. Further, the spray drift risk assessment may be impacted by those issues reviewed by the recent SAP. Accordingly, the Agency will address this claim fully when it provides its complete response in December 2012.

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<sup>3</sup> For convenience's sake, the legal requirements regarding the additional safety margin for infants and children in section 408(b)(2)(C) 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.

<sup>4</sup> Available at <http://www.regulations.gov/#!docketDetail;D=EPA-HQ-OPP-2008-0850>.

In connection with this peer review process, the Agency has recently received the final SAP report<sup>5</sup>, dated July 11, 2012. EPA will carefully review and consider the SAP's recommendations in developing the Agency's response to the remaining petition issues while also informing the final human health risk assessment for the statutorily mandated registration review program. Following EPA's complete written response to the petition, which it plans to provide petitioners by the end of this year, EPA intends to work to complete its human health risk assessment in connection with the registration review of chlorpyrifos under section 3(g) of FIFRA. That assessment will include consideration of issues not raised in the petition, including human dietary exposures from drinking water. It is important to note, however, that EPA may take regulatory action at any time if and when it determines that existing tolerances are unsafe or that chlorpyrifos presents unreasonable adverse effects on the environment.

The first section of this response provides the applicable statutory and regulatory background. The second section discusses this petition in the context of the legal framework of FIFRA and FFDCA. The third section discusses the regulatory background for chlorpyrifos. The fourth section contains EPA's response to each of the six issues identified above. The final section is the conclusion.

## I. Statutory and Regulatory Background/Framework

### A. *FFDCA/FIFRA and Applicable Regulations*

EPA establishes maximum residue limits, or "tolerances," for pesticide residues in food and feed commodities under section 408 of the FFDCA.<sup>6</sup> 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.<sup>7</sup> Monitoring and enforcement of pesticide tolerances are carried out by the U.S. Food and Drug Administration and the U.S. Department of Agriculture. Section 408 was substantially rewritten by the Food Quality Protection Act of 1996 (FQPA), which added the provisions discussed below establishing a detailed safety standard for pesticides, additional protections for infants and children, and the estrogenic substances screening program.<sup>8</sup>

EPA also regulates pesticides under the FIFRA.<sup>9</sup> While the FFDCA authorizes the establishment of legal limits for pesticide residues in food, FIFRA requires the approval of pesticides prior to their sale and distribution,<sup>10</sup> 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.<sup>11</sup> 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

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<sup>5</sup> Available at <http://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPP-2012-0040-0029>

<sup>6</sup> 21 U.S.C. 346a

<sup>7</sup> 21 U.S.C. 331, 342

<sup>8</sup> Public Law 104-170, 110 Stat. 1489 (1996).

<sup>9</sup> 7 U.S.C. 136 et seq.

<sup>10</sup> 7 U.S.C. 136a(a).

<sup>11</sup> 7 U.S.C. 136j(a)(2)(G).

risk from residues in or on food,<sup>12</sup> and directing that EPA coordinate, to the extent practicable, revocations of tolerances with pesticide cancellations under FIFRA.<sup>13</sup>

In addressing the review of petitions, however, Congress has expressly provided that any issue that can be raised through the FFDCA review process can only be reviewed through that process.<sup>14</sup> Accordingly, to the extent a petition to revoke tolerances and cancel registrations raises issues relevant to the establishment or revocation of tolerances, EPA's response to those issues may be challenged only through the administrative and judicial review procedures provided in section 408 of the FFDCA and are not reviewable under FIFRA or any other provision of law.

## II. Legal Framework and the NRDC and PANNA Petition

### A. FFDCA

All but one of the issues raised in the petition relate to EPA's establishment of tolerances under the FFDCA. For this reason, as explained in section I, the FFDCA directs that consideration of these petition issues be undertaken under FFDCA section 408. Under the FFDCA, EPA takes final action on a petition to revoke tolerances by either issuing an order in the Federal Register denying the petition or by publishing a final rule revoking the tolerances. EPA does not intend to issue a formal denial in the Federal Register for the five issues addressed in this response that are subject to FFDCA review until after it completes its review of the four remaining petition issues. That way, petitioners will not be compelled to assess whether to file objections to EPA's responses on separate occasions and EPA will not be compelled to produce separate responses. However, if petitioners wish to begin the objections process on today's partial response, EPA will publish a formal denial order for those claims. As explained previously, EPA intends to address, in writing, the remaining issues raised in the petition by December 2012. Following this written response, to the extent EPA denies the petition, EPA would expect to publish any denial order by February 2013. While the December response will address all the remaining issues raised in the petition, it is possible that EPA will not be taking final agency action on all the petition issues immediately following the December 2012 response.

While petitioners have raised a number of issues related to the assessment of the toxicity of chlorpyrifos, the petition did not address in any detail, dietary exposure to chlorpyrifos that must be taken into account in determining whether tolerances are safe. Reassessing the exposure to chlorpyrifos is one of the issues EPA intends to address in the registration review assessment of the chemical, which is currently underway. It is possible that if EPA concludes that the toxicity profile of chlorpyrifos needs to be modified based upon this reassessment, the final decision on the petition would need to wait for the conclusion of the chlorpyrifos exposure reassessment under the registration review program. The registration review assessment will include consideration of issues not raised in the petition, including human dietary exposures from drinking water. It is important to note, however, that EPA may take regulatory action at any time

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<sup>12</sup> 7 U.S.C. 136(bb).

<sup>13</sup> 21 U.S.C. 346a(l)(1).

<sup>14</sup> 21 U.S.C. 346a(h)(5); NRDC v. Johnson, 461 F.3d 164, 176 (2d Cir. 2006).

if and when it determines that existing tolerances are unsafe or that chlorpyrifos presents unreasonable adverse effects on the environment.

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.<sup>15</sup> EPA publishes in the Federal Register a notice of the petition filing and requests public comment.<sup>16</sup> After reviewing the petition, and any comments received on it, EPA may issue a final rule establishing, amending, or revoking the tolerance, issue a proposed rule to do the same, or deny the petition.<sup>17</sup>

Once EPA takes final action on the petition by establishing, amending, or revoking the tolerance or denying the petition, any party may file objections with EPA and seek an evidentiary hearing on those objections.<sup>18</sup> Objections and hearing requests must be filed within 60 days.<sup>19</sup> The statute 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.”<sup>20</sup> 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, 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.<sup>21</sup> 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.<sup>22</sup> EPA’s final order on the objections is subject to judicial review in the U.S. Court of Appeals.<sup>23</sup>

## B. FIFRA and Exporting Hazard

The exporting hazard issue raised in the petition is the sole claim that raises issues that are subject to FIFRA review. Petitioners claim that “unless chlorpyrifos is banned, and all tolerances cancelled [sic], chlorpyrifos will continue to be used, often unsafely, in other countries thus creating a health and environmental hazard in those countries and on contaminated food re-entering the US.”<sup>24</sup> While the claim includes a request to both cancel registrations and revoke tolerances, the policy arguments raised in the petition regarding the consideration of the international impacts of the U.S. registration of chlorpyrifos are not relevant to the establishment of tolerances under the FFDCA. FIFRA Section 6 authorizes EPA to cancel pesticide registrations that do not comply with FIFRA and, in certain circumstances, to suspend those registrations pending the completion of cancellation proceedings. EPA takes final Agency action

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<sup>15</sup> See 21 U.S.C. 346a(d)(1).

<sup>16</sup> 21 U.S.C. 346a(d)(3).

<sup>17</sup> 21 U.S.C. 346a(d)(4).

<sup>18</sup> 21 U.S.C. 346a(g)(2).

<sup>19</sup> *Id.*

<sup>20</sup> 21 U.S.C. 346a(g)(2)(B).

<sup>21</sup> 40 CFR 178.32(b)

<sup>22</sup> See *Nat’l Corn Growers Assoc., et al. v. EPA* 613 F.3d 266 (D.C. Cir. 2010).

<sup>23</sup> 21 U.S.C. 346a(h)(1).

<sup>24</sup> Petition at 21.

when it issues a response to petitioners either denying their petition or by initiating and completing the cancellation process under FIFRA.

EPA considers this portion of the response to NRDC's petition to be a final action, and believes the petitioner may challenge now this portion of the Agency's petition denial in federal court pursuant to section 16 of FIFRA. Because, as explained below, EPA is today denying petitioners' request to cancel on the basis of the export hazard issue, this letter will constitute a final Agency action as it relates to that specific issue. As noted, the remaining issues are subject to review as provided in section 408 of the FFDCA.

### III. Background

In 2000, the chlorpyrifos technical registrants entered into an agreement with the Agency regarding the use of chlorpyrifos which eliminated virtually all homeowner residential uses, phased-out all termiticide uses, eliminated use on tomatoes, and changed use on grapes and apples from a foliar use to a dormant use.

In September 2001, the Agency completed its IRED for chlorpyrifos. At the time of the IRED the Agency was also working on the OP CRA, which addresses all those OP pesticides sharing the common mechanism endpoint, acetylcholinesterase (AChE) inhibition. Specifically, the members of this class share the ability to bind to and phosphorylate the enzyme AChE in both the central (brain) and peripheral nervous systems.

In August 2006, the Agency released its 2006 Update to the OP CRA. With EPA's 2006 release of the OP CRA, all reregistration eligibility decisions (REDs) for individual OP pesticides, including chlorpyrifos, were considered complete. OP IREDs, therefore, were considered completed REDs.

In September 2007, EPA received NRDC and PANNA's joint petition to revoke all tolerances and cancel all registrations for chlorpyrifos. The petition largely challenged the conclusions of the Agency's IRED and 2006 OP CRA.

Although EPA completed reregistration and tolerance reassessment for the OP pesticides in 2006, the Agency made the decision to move chlorpyrifos and other OP pesticides forward in the re-evaluation schedule so that they began registration review in 2008 and 2009. The chlorpyrifos registration review docket opened in 2009.

In connection with its ongoing re-evaluation of chlorpyrifos and analyses of the complex issues raised in the petition, in 2008 EPA convened an SAP meeting to review a draft science issue paper on the human health effects of chlorpyrifos to provide a preliminary review of the scientific literature on experimental toxicology and epidemiology studies available at that time. Specifically, the focus was on studies that evaluated the effects of chlorpyrifos on infants and children from *in utero* and/or post-natal exposures and on studies that evaluated population variability with respect to response to paraxonase (PON1). In summary, the SAP expressed confidence that the studies conducted by Columbia University are epidemiologically sound. The SAP agreed with the Agency that human epidemiological studies have utility for risk

characterization, but not as the principal basis for establishing the point of departure (PoD), in part due to uncertainty in attributing observed adverse neurodevelopmental effects in children solely to chlorpyrifos, when exposure was to multiple anticholinesterase insecticides.<sup>25</sup>

In December 2009, EPA convened a SAP to review scientific issues associated with interpreting risks related to the field volatilization of conventional pesticides.<sup>26</sup> The objectives of the meeting were to review both the exposure and hazard aspects of the risk assessment process. The primary focus of the discussion on exposure assessment was on methods for predicting emissions from treated fields in lieu of having actual field volatilization studies as well as how such information should be considered in exposure assessment. With regard to hazard evaluations, the impact on inhalation risk estimates based on differences in how doses are experimentally administered to rodents (oral or inhalation) was considered. The Agency's goal for the SAP review was to receive feedback on procedures, methodologies, and data inputs to inform the assessment of bystander exposure resulting from field volatilization of conventional pesticides. The procedures, refined in part from the SAP's feedback, will inform the Agency's analysis as it considers chlorpyrifos emissions data identified in the literature, as well as data from a field study Dow Agrosiences undertook and submitted to the Agency on July 6, 2012.

In February 2010, EPA convened an SAP to review the Agency's draft "Framework for Incorporating Human Epidemiologic & Incident Data in Health Risk Assessment,"<sup>27</sup> which provides the conceptual foundation for evaluating multiple lines of scientific evidence in a human health risk assessment. This draft framework draws from the mode of action framework<sup>28</sup> and its use of the modified Bradford Hill Criteria<sup>29</sup> and, thus, explicitly considers such concepts as strength, consistency, dose response, temporal concordance and biological plausibility.

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<sup>25</sup> U.S. EPA (2008). Transmittal of Meeting Minutes of the FIFRA Scientific Advisory Panel Meeting Held September 16-18, 2008 on the Agency's Evaluation of the Toxicity Profile of Chlorpyrifos. Available at <http://www.epa.gov/scipoly/sap/meetings/2008/september/sap0908report.pdf>

<sup>26</sup> U.S. EPA (2009). Transmittal of Meeting Minutes of the FIFRA SAP Meeting Held December 1-3, 2009 on the Scientific Issues Associated with "Field Volatilization of Conventional Pesticides." Available at <http://www.epa.gov/scipoly/sap/meetings/2009/december/120309meetingminutes.pdf>

<sup>27</sup> U.S. EPA (2010). Transmittal of Meeting Minutes of the FIFRA Scientific Advisory Panel Meeting on the Draft Framework and Case Studies on Atrazine, Human Incidents, and the Agricultural Health Study: Incorporation of Epidemiology and Human Incident Data into Human Health Risk Assessment. Available at <http://www.epa.gov/scipoly/sap/meetings/2010/020210minutes.pdf>

<sup>28</sup> U.S. EPA (2007). Framework for Determining a Mutagenic Mode of Action for Carcinogenicity: Using EPA's 2005 Cancer Guidelines and Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens. Available at <http://www.epa.gov/osa/mmoaframework/pdfs/MMOA-ERD-FINAL-83007.pdf>

<sup>29</sup> U.S. EPA (1999). Guidelines for Carcinogen Risk Assessment, Risk Assessment Forum, SAB Review Draft. Available at <http://www.epa.gov/cancerguidelines/draft-guidelines-carcinogen-ra-1999.htm>; Sonich-Mullin, C., R. Fielder, J. Wiltse et al, 2001. IPCS conceptual framework for evaluating a mode of action for chemical carcinogenesis. Regul Toxicol Pharmacol. 34:146-152 Meek, M.E., J.R. Bucher, S.M. Cohen et al, 2003. A framework for human relevance analysis of information on carcinogenic modes of action. Crit. Rev. Toxicol. 33:591-653; Seed, J., E.W. Carney, R.A. Corley et al., 2005. Overview: Using mode of action and lifestage information to evaluate the human relevance of animal toxicity data. Crit. Rev. Toxicol. 35(8-9):664-672; U.S. EPA (2005). Guidelines for Carcinogen Risk Assessment. Available at [http://www.epa.gov/raf/publications/pdfs/CANCER\\_GUIDELINES\\_FINAL\\_3-25-05.PDF](http://www.epa.gov/raf/publications/pdfs/CANCER_GUIDELINES_FINAL_3-25-05.PDF)

In July 2011, the Agency released the preliminary HHRA for chlorpyrifos for public comment. The comment period officially closed on October 6, 2011. The Agency received 48 unique comments totaling over 1000 pages, which included a number of significant study citations. The Agency continues to work on reviewing the public comments and studies cited to further inform the final HHRA for chlorpyrifos.

Since the 2008 SAP on chlorpyrifos, and in part due to the SAP's feedback, the Agency has performed further analyses on the existing and new epidemiology studies with mothers and children, available biomonitoring data, and experimental toxicology studies evaluating proposed adverse outcome pathways in the context of human health risk assessment. Specifically, the Agency is evaluating available literature on the potential for chlorpyrifos to cause long term adverse effects from early life exposure, *in vivo* and *in vitro* studies evaluating mechanistic aspects of chlorpyrifos, and the potential for adverse effects below PoDs established from cholinesterase inhibition used for regulatory purposes. This analysis is complicated and multifaceted as it involves many lines of scientific evidence (i.e., *in vivo* & *in vitro* experimental toxicology studies, explicit consideration of adverse outcome pathway framework analyses, exposure, human epidemiology, and biomonitoring data). As the Agency works to finalize the HHRA and respond to the remaining petition issues, the Agency is working towards a weight of evidence evaluation integrating the epidemiology studies with the experimental toxicology studies for the neurodevelopmental outcomes. As noted previously the Agency convened a FIFRA SAP in April 2012 to review the Agency's analyses to ensure it is utilizing sound science in making its regulatory determinations and has recently received the final SAP report, dated July 11, 2012, of that meeting.

#### IV. Petition Response

##### *1. Genetic Evidence of Vulnerable Populations*

###### *a. Petitioners' claim*

Petitioners claim that the Agency failed to calculate an appropriate intra-species uncertainty factor (i.e., within human variability) for chlorpyrifos in both its aggregate and cumulative assessments.<sup>30</sup> They assert that certain relevant, robust data, specifically the Furlong et al. (2006) study<sup>31</sup> that addresses intra-species variability in the behavior of the detoxifying enzyme PON1, indicates 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.<sup>32</sup> 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.

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<sup>30</sup>Petition at 6.

<sup>31</sup>Furlong CE, Holland N, Richter RJ, Bradman A, Ho A, Eskenazi B (2006). PON1 status of farmworker mothers and children as a predictor of organophosphate sensitivity. *Pharmacogenet Genomics*. 2006 Mar; 16(3):183-90.

<sup>32</sup>Petition at 6.

## 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 pesticide 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 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. For these reasons, as further explained below, EPA believes it is not appropriate to 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. At this time, there is not a reasonable scientific basis for departing from the standard 10-fold intra-species uncertainty factor for extrapolating variability based on PON1.

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. Specifically, PON1 is an A-esterase which can metabolize chlorpyrifos oxon without inactivating the enzyme.<sup>33</sup> 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.<sup>34</sup> 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<sup>35</sup>; Chen et al., 2003).<sup>36</sup> However,

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<sup>33</sup> Sultatos LG; Murphy SD, (1983). Kinetic Analysis Of The Microsomal Biotransformation Of The Phosphorothioate Insecticides Chlorpyrifos And Parathion. *Fundamental and Applied Toxicology*. 3:16-21.

<sup>34</sup> U.S. EPA (2008). Draft Appendix E available at [http://www.epa.gov/scipoly/sap/meetings/2008/september/appendix\\_e.pdf](http://www.epa.gov/scipoly/sap/meetings/2008/september/appendix_e.pdf). Draft Science Issue Paper: Chlorpyrifos Hazard and Dose Response Characterization. August 21, 2008. Available at <http://www.epa.gov/scipoly/sap/meetings/2008/september/chlorpyrifoscharacter.pdf>

<sup>35</sup> Note, Holland et al (2006) and Furlong et al (2006) report findings from the same cohort. The Holland reference provides enzyme activities for specific polymorphisms in Table 4; the Furlong paper does not report such values and provides information primarily in graphical form.

<sup>36</sup> Holland, N., Furlong, C., Bastaki, M., Richter, R., Bradman, A., Huen, K., Beckman, K., and Eskenazi, B. (2006). Paraoxonase polymorphisms, haplotypes, and enzyme activity in Latino mothers and newborns. *Environ. Health Perspect.* 114(7), 985-991; Chen, J., Kumar, M., Chan, W., Berkowitz, G., and Wetmur, J. (2003). Increased Influence of Genetic Variation on PON1 Activity in Neonates. *Environmental Health Perspective* 111, 11:1403-9

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.”<sup>37</sup>*

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. It is noteworthy that a recent report by the CDC-ATSDR,<sup>38</sup> is in agreement with EPA’s conclusion. It states that the “correlation between PON-1 genotype, cholinesterase activity, and clinical toxicity needs to be further evaluated.” Population variability data on PON1 would be more useful incorporated into a physiologically-based pharmacokinetic model which would account for all the metabolic processes relevant for chlorpyrifos at a range of dose levels.

Since the 2008 SAP, several epidemiological studies have been published that considered the association between PON1 status/genotype and health outcome. Hofmann et al. (2009) recently reported associations between PON1 status and inhibition of butyrylcholinesterase 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.<sup>39</sup> Given the limitations of Hofmann et al.,

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<sup>37</sup> U.S. EPA (2008). Transmittal of Meeting Minutes of the FIFRA Scientific Advisory Panel Meeting Held September 16-18, 2008 on the Agency’s Evaluation of the Toxicity Profile of Chlorpyrifos. Available at <http://www.epa.gov/scipoly/sap/meetings/2008/september/sap0908report.pdf> at 61.

<sup>38</sup> Matthews, A.R., Sutter, M.E., Rentz, D.E. (2011) Serum Paraoxonase-1 (PON-1) Genotype and Exposure to Organophosphorous Insecticides—Is There a High-Risk Population? *J. Med. Toxicol.* (2011) 7:243–247 DOI 10.1007/s13181-011-0166-2.

<sup>39</sup> 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].

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 OP pesticides.<sup>40</sup> These studies (Eskenazi, et al., 2010; Harley et al., 2011; Engel et al., 2011) 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 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 guidance on chemical specific adjustment factors.<sup>41</sup> The guidance recommends 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). This is conceptually consistent with the way EPA applies the intra-species uncertainty factor. 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

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<sup>40</sup> Eskenazi, B.; Huen, K., Marks, A., Harley, K.G., Bradman, A., Boyd Barr, D., Holland, N. (2010) PON1 and Neurodevelopment in Children from the CHAMACOS Study Exposed to Organophosphate Pesticides in Utero. *Environmental Health Perspectives*. Vol 118 (12): 1775-1781; Engel, S.M., Wetmur, J., Chen, J., Zhu, C., Boyd Barr, D., Canfield, R.L., Wolff, M.S., (2011) Prenatal Exposure to Organophosphates, Paraoxonase 1, and Cognitive Development in Childhood. *Environ Health Perspect* 119:1182–1188 (2011). doi:10.1289/ehp.1003183 [Online 21 April 2011]; 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.

<sup>41</sup> IPCS (International Programme on Chemical Safety) 2005. Chemical-Specific Adjustment Factors for Interspecies Differences and Human Variability: Guidance Document for Use of Data in Dose/Concentration-Response Assessment. Harmonization Project Document No. 2. World Health Organization, International Programme on Chemical Safety, Geneva, Switzerland.

likely greatly exaggerate potential intra-species variability. That approach effectively assumes that the PoD 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. 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.<sup>42</sup> Finally, petitioners' statement that the Furlong et al. study supports an intra-species uncertainty factor of at least 150X likely overstates potential variability. While EPA does believe that further research in this area may be required, in part, because multiple factors most likely impact potential population sensitivity, at this time, there is no scientific basis for departing from the standard 10-fold intra-species uncertainty factor for extrapolating variability based on PON1. The Agency will continue to monitor the scientific literature regarding PON1. At this point in time, however, petitioners' claims regarding PON1 would not be a factor in any risk determination the Agency might make to revoke chlorpyrifos tolerances. EPA therefore intends to deny this aspect of the petition when it publishes its response to the petition in the Federal Register.

## *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<sup>43</sup> (EDSP) 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

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<sup>42</sup> *Id.*

<sup>43</sup> See <http://www.epa.gov/endo/>

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/PoDs) that indicate endocrine effects at doses that are more sensitive than the PoDs currently used in the chlorpyrifos risk assessment. 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. EPA, therefore, intends to deny this portion of the petition when it publishes its response to the petition in the Federal Register. However, because the cited literature studies provide qualitative information to screen chlorpyrifos for the potential to interact with the estrogen, androgen, and thyroid hormonal pathways, EPA will include them in its upcoming weight of evidence evaluation of chlorpyrifos under EPA's EDSP, as required by section 408(p) of the FFDCA.

As petitioners may be aware, since the filing of the petition, EPA has initiated the evaluation of chlorpyrifos under EPA's EDSP, as required under FFDCA section 408(p).

On April 15, 2009, a Federal Register notice was published in which chlorpyrifos was included in the initial list of chemicals to receive EDSP Tier 1 test orders. The EDSP program is a two-tiered screening and testing program; Tier 1 assays 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.<sup>44</sup> On February 13, 2010, EPA received the 90-day responses to the test orders. In the initial response, the test order recipients agreed to conduct 9 of the 11 assays that comprise the EDSP Tier 1 screening battery. The test order recipients also sought to rely on existing data for two of the 11 assays, the male and female pubertal assays. The Agency also received a submission from PETA and PCRM that cited existing studies that they claimed adequately fulfill the requirements of the EDSP Tier1 battery for chlorpyrifos.

On October 20, 2010, following the review of the Other Scientifically Relevant Information (OSRI) that had been submitted, EPA determined that the male pubertal assay test order was satisfied based on the OSRI submitted by PETA/PCRM; this conclusion was based on an interpretation that the data demonstrated potential interaction with the androgen and thyroid hormonal pathways.<sup>45</sup> For the female pubertal assay, however, EPA determined that the assay was still necessary because of deficiencies and unanswered questions in the studies cited in the OSRI submissions. The study deficiencies included the lack of thyroid weights and thyroid hormone measurements. In addition, organ weights and histopathology data were obtained in adult animals, whereas in the Tier 1 female pubertal assay, this data is obtained in pubertal animals.

The test order recipients disagreed with the Agency's interpretation that the OSRI submitted by PETA/PCRM demonstrated potential interaction with the androgen and thyroid hormonal pathways. Because the test order recipients disagreed with the Agency's interpretation of the data cited for the Male Pubertal Assay, they elected to conduct the full Tier 1 battery of assays. The Agency has received all 11 Tier 1 screening assays and is in the data review process. EPA intends to review these chlorpyrifos data as part of its larger process for reviewing all of the Tier 1 data submitted on List 1 EDSP chemicals.

Consistent with the recommendation of the joint Scientific Advisory Board and FIFRA SAP in 1999 (EPA-SAB-EC-00-013, July 1999), the Agency plans to conduct a mid-course review of the functionality of each assay and the battery as a whole. These performance evaluations of the Tier 1 battery will be conducted on an adequate sample of chemicals and it is further anticipated that these Tier 1 performance review results will be submitted for external scientific peer review by the FIFRA SAP in fiscal year 2013. Specifically, EPA intends to first review the data from each individual assay for several chemicals to ensure that EPA consistently interprets the measurements for particular endpoints in that assay; e.g., EPA will review the thyroid weight measurements reported in the male pubertal assays from a number of chemicals to ensure that the Agency reaches consistent conclusions as to the significance of the reported results. After that process has been completed, EPA will evaluate each chemical's response across the battery of 11 assays to determine whether there is evidence of interaction with the estrogen, androgen, and/or thyroid hormone systems.

EPA believes that the results from the entire battery of Tier 1 screening and Tier 2 testing under the EDSP program are necessary to make the statutory determination of whether a

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<sup>44</sup> See <http://www.epa.gov/endo/pubs/toresources/index.htm> for information related to the status of EDSP test orders/DCIs, status of EDSP OSRI: order recipient submissions and EPA responses, and other EDSP assay information.

<sup>45</sup> See <http://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPP-2009-0634-0159>.

substance may have an effect similar to an effect produced by a naturally occurring hormone (FR Vol, 63, No. 248/Monday December 28, 1998). In other words, a positive result in the Tier 1 screening assays would not be sufficient to make the determination of whether chlorpyrifos interacted with the endocrine system. The citations included in the petition referred to as evidence that chlorpyrifos may affect estrogen, androgen, and thyroid hormonal pathways do not establish quantitative, dose-response relationships for potential endocrine effects, which is the purpose of Tier 2 testing.

The information cited in the petition will be considered along with all other information submitted to the Agency by either the test order recipient or the public, including the information already submitted by the petitioners, using a weight-of-evidence (WoE) approach consistent with the Agency's September 14, 2011 EDSP WoE guidance.<sup>46</sup> Based on this WoE assessment, EPA will determine whether chlorpyrifos has the potential to interact with hormone pathways and, if so, whether any Tier 2 or other, more targeted testing, is required to confirm interaction with specific hormone systems and to characterize any potential effects identified through Tier 1 screening, and to establish the dose response relationships for adverse effects necessary to conduct a quantitative risk assessment.

In summary, EPA believes that evaluating all of the evidence with respect to chlorpyrifos's potential for endocrine disruption through the Agency's standard EDSP process, as explained above, is the appropriate approach to address petitioners' request that EPA incorporate endocrine effects into its risk assessment for chlorpyrifos. This is a transparent and scientifically sound process that has been the subject of external peer review<sup>47</sup> and is designed to ensure that all data are appropriately considered. By relying on this robust scientific process, EPA believes that it will ultimately reach a final, scientifically credible determination more efficiently than if EPA were to conduct repeated reviews of the data in piecemeal and without context.

### 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)<sup>48</sup> that evaluated the association between chlorpyrifos and lung cancer incidence.<sup>49</sup> 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

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<sup>46</sup> U.S. EPA (2011), Endocrine Disruptor Screening Program: Weight-of-Evidence: Evaluating Results of EDSP Tier 1 Screening to identify the Need for Tier 2 Testing. Available at <http://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPPT-2010-0877-0021>

<sup>47</sup> See Scientific Advisory Panel, 2008 SAP Meetings, March 25-28, 2008: Review the Endocrine Disruptor Screening Program (EDSP) Proposed Tier-1 Screening Battery. Available at [http://www.epa.gov/scipoly/sap/meetings/2008/032508\\_mtg.htm](http://www.epa.gov/scipoly/sap/meetings/2008/032508_mtg.htm)

<sup>48</sup> Lee WJ, Blair A, Hoppin JA, Lubin JH, Rusiecki JA, Sandler DP, Dosemeci M, Alavanja MC. (2004) Cancer incidence among pesticide applicators exposed to chlorpyrifos in the Agricultural Health Study. *J Natl Cancer Inst*, 96(23), 1781-1789. (hereinafter Lee et al. 2004).

<sup>49</sup> Petition at 10

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 revocation of tolerances or 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, when EPA publishes its response to the petition in the Federal Register, EPA intends to deny the petitioners’ request to revoke chlorpyrifos tolerances or cancel chlorpyrifos registrations to the extent that request 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,<sup>50</sup> 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.<sup>51</sup> 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<sup>52</sup> cited by the petitioners. As noted below, both the Agency and Health Canada have comprehensively reviewed these data. Further, the Agency has

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<sup>50</sup> U.S. EPA (2011). Christenson Memorandum “Chlorpyrifos Carcinogenicity: Review of Evidence from the U.S. Agricultural Health Study (AHS) Epidemiologic Evaluations 2003-2009. (hereinafter Christenson 2011).

<sup>51</sup> Lee et al. 2004 at 1788.

<sup>52</sup> Lee et al 2004.

proposed a draft framework<sup>53</sup> to consider epidemiologic information in the risk assessment process, and additionally utilized AHS data in a case study illustrating the similarities and differences in exposure assessment methodology between epidemiologic research and regulatory risk assessment.

In accordance with the Agency's 2005 Guideline for Cancer Risk Assessment,<sup>54</sup> 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.<sup>55</sup> 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)<sup>56</sup> recently 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. The Agency will continue to review additional AHS data as well as other epidemiologic evaluations during the development of the HHRA.

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.

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<sup>53</sup> U.S. EPA Presentation to the FIFRA Science Advisory Panel, February 2010. Available at <http://www.epa.gov/scipoly/sap/meetings/2010/020210meeting.html#materials>.

<sup>54</sup> U.S. EPA (2005). Guidelines for Carcinogen Risk Assessment. Available at [http://www.epa.gov/raf/publications/pdfs/CANCER\\_GUIDELINES\\_FINAL\\_3-25-05.PDF](http://www.epa.gov/raf/publications/pdfs/CANCER_GUIDELINES_FINAL_3-25-05.PDF).

<sup>55</sup> Christenson 2011.

<sup>56</sup> Weichenthal S, Moase C, Chan P (2010). A review of pesticide exposure and cancer incidence in the agricultural health study cohort. *Cien Saude Colet.* 2012 Jan;17(1):255-70. PubMed PMID: 22218559.

#### 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 CRA.<sup>57</sup> Specifically, the petitioners challenge the Agency's use of data from a paper by Zheng et al. (2000)<sup>58</sup> 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.<sup>59</sup> 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 OP pesticides. Petitioners have not made such a showing. For this reason, when EPA publishes its response to the petition in the Federal Register, EPA intends to deny 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 OP CRA based on the results of the Zheng et al. study.

Despite the inadequacy of petitioners' FQPA safety factor claims, EPA has 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 action that might lead to revocation of the chlorpyrifos tolerances.

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 is cholinesterase inhibition, the primary toxicity mode of action and the most sensitive, quantifiable endpoint for the OP pesticides. As such, for the OP CRA, experimental toxicology data on AChE inhibition are used for developing relative potency estimates, PoDs, and informing the FQPA safety factor. EPA has relied on brain AChE data from adult female rats dosed for 21 days or longer for estimating relative potency and PoDs. At approximately three weeks of oral exposure to OP pesticides, 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.

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<sup>57</sup> Petition at 16.

<sup>58</sup> Zheng Q, Olivier K, Won YK, Pope CN. 2000. Comparative cholinergic neurotoxicity of oral chlorpyrifos exposures in preweaning and adult rats. *Toxicological Sciences*, 55(1): 124-132.

<sup>59</sup> Petition at 14.

The Agency's 2006 OP CRA contains EPA's complete FQPA safety factor analysis,<sup>60</sup> 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 are not expected to underestimate exposure to OP pesticides.

In the CRA, each OP pesticide 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 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, who is also a member of the FIFRA SAP, 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 OP pesticides a benchmark dose (BMD) 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, in 2006 the Agency was confident in the value used. Since that time, the Agency attempted BMD modeling of the Zheng et al. data as part of the 2011 preliminary chlorpyrifos HHRA<sup>61</sup> which yielded low confidence results due to the variability in the data

Dow AgroSciences recently submitted a new 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 (PND) 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

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<sup>60</sup> Available at [http://epa.gov/pesticides/cumulative/2006-op/op\\_cra\\_main.pdf](http://epa.gov/pesticides/cumulative/2006-op/op_cra_main.pdf).

<sup>61</sup> U.S. EPA (2011). Chlorpyrifos: Preliminary Human Health Risk Assessment for Registration. Available in docket number EPA-HQ-OPP-2008-0850, <http://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPP-2008-0850-0025>.

repeated dosing portion of the study, the BMD<sub>10s</sub> of 0.80 (0.69 BMDL<sub>10</sub>) and 1.0 (0.95 BMDL<sub>10</sub>) mg/kg/day respectively for female pups and adults results support the FQPA safety factor of 1X used in the 2006 OP CRA. Therefore, the Agency remains confident in the FQPA safety factor of 1X used in the cumulative risk assessment for chlorpyrifos. As such, petitioners' claims regarding the OP CRA and FQPA safety factor, at this time would not be a factor in a determination by the Agency to revoke tolerances for chlorpyrifos.

## 5. *Over-reliance on registrant data*

### *a. Petitioners' Claim*

Petitioners assert that 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.”<sup>62</sup> As such, the Agency’s reassessment decision is not scientifically defensible.<sup>63</sup>

### *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 their 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 has “over-relied” on registrant data in evaluating the risks of chlorpyrifos or other pesticides.

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.<sup>64</sup>

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

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<sup>62</sup> Petition at 16.

<sup>63</sup> *Id.*

<sup>64</sup> See <http://www.epa.gov/opp00001/science/guidelines.htm> for information on EPA’s Harmonized Test Guidelines and international efforts at harmonization.

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. This information is discussed in the 2008 chlorpyrifos SAP paper and the chlorpyrifos 2011 preliminary HHRA.

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 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 unfounded and not supported by the record and as such, it would form no basis of the Agency's decision to revoke chlorpyrifos tolerances or cancel chlorpyrifos registrations.

## 6. *Export Hazard*

### *a. Petitioners' claim*

Petitioners assert that EPA must ban chlorpyrifos and cancel all tolerances because, otherwise, chlorpyrifos will continue to be used unsafely by workers, including children, in other countries who may not utilize worker protection equipment required for use in the U.S.<sup>65</sup> In addition, petitioners assert that continued chlorpyrifos use internationally presents a health hazard from contaminated food re-entering the United States.<sup>66</sup>

### *b. Agency Response.*

The Agency takes very seriously its leadership role and commitment to international efforts to promote the safe use of pesticides. EPA's principal goal in international pesticide activities is to improve the protection of public health and the environment throughout the world.<sup>67</sup> Under FIFRA and FFDCA, however, EPA's primary focus in regulating pesticides is to address risk from domestic use of pesticides and from pesticide residues on imported food. It is far from clear that EPA has any authority under FIFRA to address the risks to foreign workers

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<sup>65</sup> Petition at 21.

<sup>66</sup> *Id.*

<sup>67</sup> EPA actively participates in Codex, which is a joint food standards program of the United Nations Food and Agriculture Organization (FAO) and the World Health Organization (WHO). Codex develops international food safety and quality standards, including Maximum Residue Limits (MRLs) for pesticides. EPA contributes technical expertise to the development of these standards and related policies. Additional information can be found at [http://www.codexalimentarius.net/web/index\\_en.jsp](http://www.codexalimentarius.net/web/index_en.jsp). EPA is also active in the Organization for Economic Co-operation and Development (OECD) Working Group on Pesticides. The objective of the OECD Pesticide Program is to help governments co-operate in assessing and reducing the risks of agricultural pesticides. Additional information on the OECD pesticide program can be found at [http://www.oecd.org/document/34/0,3746,en\\_2649\\_37465\\_48447010\\_1\\_1\\_1\\_37465,00.html](http://www.oecd.org/document/34/0,3746,en_2649_37465_48447010_1_1_1_37465,00.html).

who may not be utilizing the protective equipment that EPA requires when a pesticide product is used within EPA's jurisdiction. Further, to the extent that EPA could in some limited fashion take international considerations into account under its authorities, it is extremely difficult to predict what the effects would be internationally from a U.S. ban on chlorpyrifos use because a U.S. ban does not legally limit either the export of cancelled pesticides from the U.S. or the manner of their use overseas. Section 17 of FIFRA (7 U.S.C. 136o), and EPA regulations at 40 C.F.R. Part 168 Subpart D have specific requirements that apply to the export of unregistered pesticides, but these provisions do not provide EPA with authority to ban the export of cancelled pesticides.

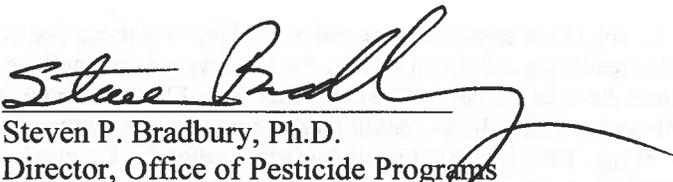
In addition to concerns about international workers, petitioners claim that if the Agency does not revoke all tolerances for chlorpyrifos, contaminated food will enter the U.S. The FFDCA specifically requires EPA to establish maximum permissible residue levels (tolerances) for pesticides only when such residues have been deemed "safe" within the meaning of section 408(b)(2)(A)(ii) (21 U.S.C. 346a(b)(2)(A)(ii)). These domestic tolerances also serve as tolerances for food imported into the U.S. The risk from the domestic use of chlorpyrifos and from residues of chlorpyrifos on imported food will be addressed by the Agency's final response to the petition and EPA's final HHRA. If EPA determines in that process that there is an unsafe risk from chlorpyrifos in food, the Agency will revoke tolerances as necessary. This action would obviously limit chlorpyrifos' use overseas on crops bound for the U.S. and, thus, would likely limit chlorpyrifos use internationally to some extent. But again, EPA has no authority to ban the export of cancelled pesticides.

In conclusion, there is no substantive information in petitioners' export hazard assertion that provides a basis for the cancellation of all chlorpyrifos registrations or the revocation of all chlorpyrifos tolerances.

## V. Conclusion

The Agency has carefully considered the six petition claims addressed in this response and has determined that none of these claims warrants revoking tolerances or canceling registrations for chlorpyrifos at this time. This response does not constitute a final Agency action to petitioners' request to revoke all tolerances for chlorpyrifos.

This response does, however, constitute EPA's final action on the petition's sole FIFRA issue, exporting hazard. As such, I hereby deny petitioners' claim to cancel all chlorpyrifos registrations based upon the exporting hazard claim.

  
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