Dow AgroSciences LLC's Comments on 2016 Notice of Data Availability, Revised Human Health Risk Assessment and Refined Drinking Water Assessment for Chlorpyrifos

(EPA Docket: EPA-HQ-OPP-2015-0653)

AUTHOR(S)

G. Oliver, C. Burns, D. Juberg, K. Hastings, K. Racke, P. Haven

STUDY COMPLETED ON

January 17, 2017

SUBMITTED BY:

Dow AgroSciences LLC
9330 Zionsville Road
Indianapolis, Indiana 46268-1054

TABLE OF CONTENTS

Page

TABLE OF CONTENTS
(continued)

Page

TABLE OF CONTENTS
(continued)

Page

TABLE OF CONTENTS
(continued)

Page

I. Introduction

Dow AgroSciences LLC ("DAS") respectfully submits these comments on the Chlorpyrifos: Tolerance Revocations; Notice of Data Availability and Request for Comment (EPA-HQ-OPP-2015-0653-0402), published in the Federal Register, 18 Fed. Reg. 81,049 (Nov. 17, 2016), and accompanying assessments including, specifically, the Chlorpyrifos Revised Human Health Risk Assessment for Registration Review (the "2016 RHHRA"), EPA-HQ-OPP-2015-0653-0454 (Nov. 3, 2016), and the Chlorpyrifos Drinking Water Assessment for Registration Review, EPA-HQ-OPP-2015-0653-0437 (Apr. 14, 2016). In addition to the information submitted here, DAS incorporates by reference and seeks Agency review of all prior DAS comments and other submissions as listed in Appendix A.

A. Background on Chlorpyrifos

Chlorpyrifos is an organophosphorus ("OP") insecticide first registered in the United States in 1965. Products containing chlorpyrifos protect more than fifty valuable U.S. food crops from destruction due to a variety of insect pests. Key crop uses include citrus fruits, corn, cotton, soybeans, sugarbeets, and wheat. Chlorpyrifos is one of the most widely used insecticides in the world, with approved uses in approximately 100 countries. The sustained importance of chlorpyrifos for global insect pest management is due to its outstanding efficacy and favorable environmental and human health characteristics. Revocation of chlorpyrifos tolerances would have severe negative economic impacts on American agriculture and global trade and therefore should be considered a significant regulatory action.

Chlorpyrifos is highly effective in controlling a broad spectrum of both foliar-feeding and soil-dwelling insect pests, and its important role in resistance management and integrated pest management ("IPM") programs is widely recognized. The widespread international registration approvals for chlorpyrifos and establishment by the Codex Alimentarius Commission of more than fifty international maximum residue limits ("MRLs") for chlorpyrifos residues on food crop commodities have facilitated global free trade of treated crops.

Chlorpyrifos exhibits moderate mammalian toxicity (WHO Hazard Class II) and is not carcinogenic, a selective reproductive or developmental toxicant, or an endocrine disruptor. Inhibition of blood cholinesterase has been used by EPA as a protective regulatory health

endpoint, or point of departure ("PoD"), for risk assessment for over forty-five years.[1] Use of this endpoint was recently confirmed by the European Food Safety Authority ("EFSA") and also remains the gold standard and point of departure used by the World Health Organization and virtually all major global regulatory authorities.

Chlorpyrifos is biodegradable and has only short-to-moderate persistence in most environmental settings. In terrestrial ecosystems, chlorpyrifos rapidly dissipates from plant foliage (half-lives of <1–7 days). Soil surface half-lives are typically on the order of a few days to two weeks, whereas subsurface chlorpyrifos may demonstrate dissipation half-lives of one to two months. In aquatic ecosystems, chlorpyrifos dissipates very rapidly (half-life <24 hours) from the water column, and dissipation from sediments is similar to that observed for soils.

B. Regulatory History

In 2006, chlorpyrifos successfully completed EPA's Reregistration program under the Federal Insecticide, Fungicide, and Rodenticide Act ("FIFRA") and the Federal Food, Drug, and Cosmetic Act ("FFDCA").[2] Reregistration was a comprehensive review of the human health and ecological effects of pesticide products that ensured that they met current scientific and regulatory standards and addressed any potential concerns that might have been raised by new research since the previous regulatory review. As a result of Reregistration, EPA determined that chlorpyrifos continued to meet strict safety standards, and all existing agricultural uses were reauthorized. Reregistration is followed every fifteen years by Registration Review of pesticide products pursuant to FIFRA in order to maintain confidence over the long run that the products continue to meet current standards.

In 2007, the Pesticide Action Network of North America and the Natural Resources Defense Council filed a petition with the Agency seeking to revoke tolerances and cancel the EPA registrations for chlorpyrifos (the "Petition").[3] The Petition was based in significant part on

[1] A point of departure is a dose estimate developed from experimental or observational data on a particular health effect.

[2] EPA regulates pesticides under a comprehensive, science-based regime pursuant to its authority under FIFRA and FFDCA.

[3] Under Section 408 of the FFDCA, as amended by the Food Quality Protection Act ("FQPA"), before a pesticide may be used on any food crop, EPA specifies the maximum amount of pesticidal residue (called a "tolerance") that may legally remain in or on foods. *See* 21 U.S.C.

a taxpayer-funded epidemiology study conducted by researchers at Columbia University (the "Columbia study") and first published in 2002. The Columbia study associated *de minimis* amounts of chlorpyrifos allegedly found in the umbilical cord blood of a group of mothers almost twenty years ago with neurodevelopmental effects allegedly found in their children later in life. In response to the Petition, EPA initiated the Registration Review of chlorpyrifos—even though the Agency was not statutorily required to complete another review of chlorpyrifos until 2022. As part of Registration Review, EPA conducted multiple risk assessments and convened several sessions of its FIFRA Scientific Advisory Panel ("SAP") to evaluate the Columbia study and other epidemiology studies as well as the Agency's draft framework for integrating epidemiology in risk assessment. The SAPs expressed significant concerns about the quantitative use of the Columbia study in risk assessment. Overall, the reports from these SAP meetings do not support the position that the Columbia study justifies disregarding over forty years of toxicological data that demonstrate the adequacy and protectiveness of the current regulatory standard.

Still not satisfied with EPA's efforts, the petitioners asked the U.S. Court of Appeals for the Ninth Circuit to force EPA to make a decision on the Petition. During these proceedings, EPA notified the court in March 2015 that it intended to deny the Petition, confirming the Agency's confidence in the current regulatory standard for chlorpyrifos and the rigorous toxicology data supporting that standard.[4]

EPA then abruptly changed course and advised the court in June 2015 that it intended to *grant* the petition by seeking revocation of all tolerances, citing purported drinking water exposure concerns (not even raised in the Petition) that the Agency was working to address. The court granted the petitioners' request and has set March 31, 2017, as the final deadline for EPA to make a decision on the Petition.

Instead of completing Registration Review, EPA issued a proposed rule on November 6, 2015, to revoke all tolerances previously established for food uses of chlorpyrifos, 80 Fed. Reg. 69,087 (Nov. 6, 2015) (the "Proposed Rule"). EPA's proposed revocation of tolerances would

---

§346a. Without the requisite food safety tolerances, EPA would be required to cancel the underlying registrations for those uses.

[4] Status Rep., *In re Pesticide Action Network N. Am. v. U.S. EPA,* No. 14-72794 at 2 (9th Cir. Mar. 31, 2015), ECF No. 14 at 2.

effectively end most chlorpyrifos uses, including current uses on all crops in U.S. agriculture. The Proposed Rule was based, in part, on the Agency's admittedly incomplete drinking water assessment and, in part, on the Columbia study. Despite repeated requests, and the fact that the Columbia study was federally funded, the researchers have refused to make the full raw dataset from the study available for review and validation.

Undeterred by the prior SAPs' admonitions, the Agency went back to the SAP in the spring of 2016 with a proposal for a new regulatory standard for chlorpyrifos based directly on cord blood concentrations reported in the Columbia study. But the 2016 SAP rejected EPA's approach, deeming the Columbia study insufficient for quantitative use in risk assessment, citing numerous deficiencies in the study (including as to the validity and reliability of the reported test results), and expressing concerns with EPA's reliance on the study in the absence of the raw data. While the Agency maintained that being published in scientific journals was adequate validation of the Columbia study, the SAP countered that such peer review cannot be equated to a study conducted under Good Laboratory Practices ("GLPs"), which is a required condition of studies by registrants, especially when measurements and conclusions have not been independently replicated. The SAP was especially concerned about the "immense ramifications" that EPA's proposed deficient approach would have on U.S. agriculture. Not surprisingly, many of these concerns echoed the criticisms of the prior SAPs.

The shift to a reliance on the Columbia study to set a PoD did not reflect the emergence of new information. Columbia researchers started publishing in 2002 on exposure, with the infant outcome studies first appearing in 2004. EPA was therefore aware of the Columbia study results when it reaffirmed the current PoD based on cholinesterase inhibition as the appropriate and protective PoD several times, including as recently as December 2014. SAPs convened during that time period also supported the continued use of cholinesterase inhibition as the PoD.

In its current RHHRA, EPA is now advancing yet another new regulatory standard that hypothesizes (without factual support) as to how subjects in the Columbia study may have been exposed to just the right amount of chlorpyrifos in their homes to have resulted in the very low doses that allegedly caused neurodevelopmental effects that just a few months ago the Agency was attempting to support by reference to the cord blood data. But the SAP's conclusion that the cord blood test results reported in the Columbia study are not reliable means that the conclusions

reached in that study based on those test results are also not reliable. ***In other words, since the Columbia researchers' published conclusions are directly dependent on the cord blood testing that the SAP has found invalid and unreliable, EPA should not be relying on the Columbia study for any purpose*** related to regulatory decision-making. The 2016 RHHRA also lacks any definition of the specific neurodevelopmental effects allegedly caused by the theoretical exposures assumed by EPA and to be used as the new benchmark health effect. EPA speculates that these neurodevelopmental effects claimed to be associated with chlorpyrifos are caused by some mode of action other than cholinesterase inhibition. But EPA admits no such mode of action has been identified or validated. In addition, while EPA is claiming that animal studies increasingly show effects below the current PoD, EPA does not provide credible citations for such evidence in the RHHRA to allow independent peer review and comment. No SAP has ever considered let alone endorsed EPA's new precedent-setting approach.

EPA's proposed regulatory action also still relies on an overly conservative, screening-level drinking water assessment that is not adequately refined and far over-estimates levels found in the real world. Moreover, EPA's drinking water assessment ignores important, science-based refinements that DAS provided in a study submitted to the Agency in February 2016 and in comments submitted to previous dockets by DAS and other experts.

C. EPA's Regulatory Action for Chlorpyrifos Has Compromised Principles of Sound Science and Undermined Public and Stakeholder Confidence in the Regulatory Process.

Until now, EPA has developed its human health risk assessments for crop protection tools like chlorpyrifos by using the National Research Council's four-step process recommended for all regulatory agencies in 1983: (1) hazard identification, which examines whether a substance has the potential to cause harm to humans and if so, under what circumstances; (2) dose-response assessment, which analyzes the relationship between exposure and effects; (3) exposure assessment, which evaluates the frequency, timing and levels of contact with a substance; and (4) risk characterization, which explores how well the data support conclusions about the nature and extent of the risk assessment from exposure. Pursuant to EPA policies and statutory directives, this process is to be carried out in a transparent manner and based on valid, reliable, and replicable science.

But in the case of chlorpyrifos, EPA has not sufficiently or transparently addressed any of these elements and certainly has not done so on the basis of valid, reliable, and replicable data. The Agency has departed radically from its long-standing use of animal data to rely on a single epidemiological study for use in its risk assessment, notwithstanding the Agency's lack of access to the raw data supporting the study's conclusions. In doing so, EPA has cast aside dozens of toxicology studies generated over the last forty-five years, and disregarded other epidemiology studies—many done since the Columbia study—that do not support the Columbia researchers' conclusions. EPA has also been inconsistent in its recent regulatory actions with respect to chlorpyrifos, frequently shifting its conclusions and rationale. EPA's arbitrary and capricious approach is devoid of an adequate scientific basis, contravenes EPA's own process, statutory directives, and guidance, and has no place in 21st century risk assessment or regulatory decision-making.

EPA's actions also violate Due Process. Pesticide registrants are expected to retain all raw data and make them available to EPA for any study they submit. Not holding Columbia researchers to the same standard creates a glaring inconsistency and deprives DAS and other stakeholders assurance that the underlying raw data have been appropriately reviewed and the study's conclusions appropriately validated. EPA has also violated Due Process by failing to address voluminous comments already submitted by DAS, the U.S. Department of Agriculture ("USDA"), and other stakeholders in response to EPA's prior assessments and Proposed Rule. Indeed, DAS has submitted five separate sets of comments (four in 2016 alone) to which EPA has yet to respond.

The circumstances surrounding EPA's decision-making with respect to chlorpyrifos lead DAS to the unfortunate but inescapable conclusion that EPA changed its view on this critical agricultural tool not because of any new science relating to the product, but because of an abrupt and unprecedented change in regulatory policy during the late spring of 2015. That change in policy has driven the Agency's interpretation of science, instead of, more properly, good science leading to sound public policy. What has emerged is a series of inappropriate efforts by EPA to interpret the Columbia study in unprecedented, unsupportable, and invalidated ways that are not consistent with sound scientific methodology. EPA's 2016 RHHRA and drinking water analysis represent its latest efforts to inappropriately force science into a predetermined policy outcome. After decades of allowing growers to control pests on critical crops efficiently and safely, the

Agency has set a goal—the elimination of chlorpyrifos—and then manipulated a study never designed to drive the science on this issue in an effort to achieve that goal. This is inconsistent with good science and appropriate regulatory decision-making, and contrary to law.

Additionally, it appears that the Ninth Circuit's deadline for EPA to act on the Petition has given the Agency a convenient excuse to abandon Registration Review and favor expediency over established, scientifically sound analysis mandated by statute in order to implement its policy shift on chlorpyrifos. In its Proposed Rule and during the 2016 SAP proceedings, EPA repeatedly stated that it needs to act quickly in light of the court's approaching deadline. All evidence suggests that the Agency has been driven by this deadline, not by science-based decision-making pursuant to Registration Review.

The court's deadline, however, is not a reason for the Agency to rely on a study that is invalid for regulatory decision-making, and to conduct a less than robust drinking water assessment that ignores critical input. Simply stated, neither EPA's policy shift nor the court's deadline sanction arbitrary and capricious decision-making, the violation of the Due Process rights of DAS and other adversely affected parties, and the elimination of a critical tool for growers that has been supported for decades by robust toxicology data. But that is exactly what is occurring.

Instead of compromising its scientific standards and principles of sound government in order to appease the petitioners, EPA should have denied the Petition a long time ago and proceeded in conducting its risk assessment for chlorpyrifos in accordance with its scientifically sound historical practice.

Respectfully, EPA should deny the Petition and complete FIFRA's Registration Review process for chlorpyrifos, including the human health risk assessment, based on reliable, valid, and replicable data developed under established scientific standards, including the availability of the raw data. At the very least, EPA must delay a final action on chlorpyrifos until it has obtained independent SAP reviews of its unprecedented 2016 RHHRA and drinking water assessment.

II. Executive Summary

Expanding on the foregoing Introduction, for over forty-five years, EPA has set a PoD for chlorpyrifos based on cholinesterase inhibition and currently uses Red Blood Cell cholinesterase ("RBC ChEI").[5] This conservative and health-protective endpoint remains the gold standard used by regulatory bodies around the world, including EFSA and the World Health Organization. Numerous SAPs convened by EPA over the past eight years have confirmed their confidence in RBC ChEI as the appropriate regulatory standard. *See infra,* Section III.

In a radical shift in 2016, EPA instead proposed to set a PoD based on cord blood levels of chlorpyrifos reported in the Columbia study. The Agency convened an SAP meeting in April 2016 to review and comment on its unprecedented proposal. But the 2016 SAP rejected EPA's approach, concluding that cord blood measurements at birth were an insufficient basis to establish a PoD: "the majority of the Panel considers the Agency's use of the results from a single longitudinal study to make a decision with immense ramifications based on the use of cord blood measures of chlorpyrifos as a PoD for risk assessment as premature and possibly inappropriate." EPA, Transmittal of Meeting Minutes of the April 19–21, 2016 FIFRA SAP Meeting Held to Consider and Review Scientific Issues Associated with "Chlorpyrifos Analysis of Biomonitoring Data" ("2016 SAP Minutes"), at 18–19 (July 20, 2016). The SAP also expressed concerns with the lack of access to the underlying raw data supporting the study's conclusions, the lack of validation and replication of study results, the absence of practices to ensure the credibility of the research, and questionable approaches in analyses of the data. The Panel also questioned the underlying biological plausibility of a causal link between chlorpyrifos and the health effects, noting the Panel is not aware of any scientific evidence where such extremely small levels of chlorpyrifos in the blood reported in the Columbia study would lead to deleterious neurotoxicological effects in a mammalian system. *Id.* at 23. Many of these concerns with the Columbia study and the Agency's reliance on the study for unprecedented regulatory action have

[5] Acetylcholinesterase ("AChE") inhibition ("ChEI") is the mode/mechanism of action for effects to the mammalian system. EPA regulates on a particular type of AChE which is Red Blood Cell Acetylcholinesterase ("RBC AChE") inhibition, or simply Red Blood Cell cholinesterase ("RBC ChE") inhibition. RBC ChE inhibition is not an adverse effect in itself, but a marker of exposure and a conservative and protective endpoint that occurs well below levels required to inhibit other types of AChE that could be considered an adverse health effect.

been echoed by prior SAPs and other scientific experts and federal agencies. *See infra,* Section IV, and Appendix B, Deficiencies in the Columbia Study for Purposes of Risk Assessment.

Now, EPA's 2016 RHHRA advances yet another, completely new regulatory standard that is also based principally on the Columbia study. EPA's claimed justification for its new proposal is unsupported, not validated, and significantly overstates the SAP's conclusions. In particular, as support for its decision to propose a new regulatory standard for chlorpyrifos because of concerns over neurodevelopmental effects that allegedly occur at exposures below the current regulatory endpoint of 10% RBC ChEI inhibition, EPA claims that animal studies show effects below this threshold. But EPA has provided no credible support for this assertion and indeed, DAS has submitted to the Agency GLP-compliant animal data demonstrating *no effects* below the 10% RBC ChEI inhibition standard. Moreover, EPA's position that epidemiology studies, including the Columbia study, "suggest there is evidence" for adverse health outcomes purportedly associated with chlorpyrifos at exposures below levels that result in 10% RBC ChEI inhibition does *not* demonstrate causation at those levels and should not form the basis for precedent-setting regulatory action. *See infra,* Section V.

To be clear, nothing about the science being used as the primary underpinning of EPA's new approach—the Columbia study—has changed since EPA's last proposal that was rejected by the SAP. Instead, the Agency is proposing a new hypothesis that makes unsupported assumptions about how the subjects of the Columbia study *may* have been exposed to extremely small amounts of chlorpyrifos in their homes, but yet enough to result in the neurodevelopmental effects alleged in the study. The exposure assumptions the Agency now uses, however, are not validated and the claim of a causal linkage to neurodevelopment effects at exposure levels below the current regulatory standard is still unsupported by the science. *See infra*, Section VI.

Moreover, as set forth herein, there are a number of additional fundamental issues with EPA's new regulatory standard that raise significant scientific, policy, and legal concerns. First and foremost, EPA's approach is improperly founded on its unsupported assumption that there is a *causal* link between chlorpyrifos exposure below the current regulatory level and the neurodevelopmental effects reported in the Columbia study. With this assumption in place, EPA attempts to "calculate" the level of exposure that allegedly caused these effects, using assumptions about "crack and crevice" chlorpyrifos use nearly twenty years ago. However, in

doing so, EPA ignores the opportunity to compare this calculated level of exposure with data from multiple studies in which biomonitoring followed crack and crevice applications and which would be the accepted scientific practice for validation. Since the Agency's entire analysis rests on the Columbia study's published findings (which are in turn based on cord blood data the SAP deemed unreliable), the Agency's conclusions cannot stand. *See infra,* Section VI.A. The Agency's analysis also rests on unsupported and hearsay assumptions about chlorpyrifos use that grossly misrepresent exposure. *See infra*, Section VI.B.

In addition, EPA's calculation of a single value as the time-weighted average ("TWA") blood concentration discards the Columbia researchers' division of the study subjects into two "higher" and "lower" exposure groups and conclusion that subjects exposed to higher amounts of chlorpyrifos were more likely to demonstrate neurodevelopmental effects. EPA's present analysis based on assuming all receiving a crack and crevice treatment were exposed to the level causing the claimed effects thus concedes that there is no quantitative difference between the "higher" and "lower" exposure groups, and therefore there is no dose-response relationship attributable to chlorpyrifos. Without a valid dose-response relationship, the Agency remains unable to derive a plausible PoD for risk assessment purposes. *See infra,* Section VI.C.

Even though EPA claims that its new approach responds to the SAP's recommendations, EPA has taken significant leaps from what the SAP actually advised and taken a number of the SAP's key conclusions and recommendations out of context and ignored others. For example, EPA states that its latest TWA approach, a "hybrid approach" according to the Agency, is based on a recipe that the 2016 SAP provided. But that is simply incorrect, as the transcript from the SAP proceedings (submitted by DAS to NODA docket EPA-HQ-OPP-2015-0653) shows. *See infra*, Section VI.D.

In 2016, EPA proposed to the SAP that 2% reduction in working memory was the neurodevelopment effect that would be used as the health effect endpoint to be used to set the PoD. The SAP seriously challenged the significance of that level of reduction in working memory. In the RHHRA, EPA no longer cites that as the endpoint, but now does not even define the specific neurological effect being used. Defining a specific adverse outcome for specific dose level is the hallmark of regulatory risk assessment. *See infra,* Section VI.E.4.

In addition, EPA touts that its methodology is consistent with a "weight-of-the-evidence" approach, but then ignores over forty years of robust animal toxicology data, fails to acknowledge inconsistencies and even conflicting results across epidemiology studies, and improperly downplays epidemiology studies that reach a contrary conclusion. EPA has also failed to establish basic criteria to evaluate the credibility of the epidemiology it relies upon to develop a new regulatory standard—a fundamental failure noted by at least two SAPs. *See infra*, Sections VI.E.

EPA also must seek peer review on its new, precedent-setting regulatory standard, pursuant to statutory directives and Agency guidance. Taking final action in the absence of independent peer review raises further, significant Due Process concerns and would constitute arbitrary and capricious action. *See infra,* Section VI.F.

Further, EPA's continued use of the study without the underlying raw data, which the Columbia researchers have steadfastly refused to provide, is arbitrary and capricious under well-settled case law, does not meet fundamental standards of Due Process, and contravenes EPA's statutory obligations and Executive Branch directives. *See* Appendix C, Requests for Raw Data and Expressions of Concern About Absence of Raw Data. DAS and other stakeholders have submitted numerous prior comments to EPA on these issues, which the Agency has failed altogether to address. *See infra,* Section VII.; *see also* Appendix A. EPA's new PoD is unrealistically low and results in risk estimates that have no basis in fact. This is not surprising, however, given that the PoD determination was based on a fundamentally flawed TWA approach, unsupported assumptions about crack and crevice applications, and other serious deficiencies. *See infra,* Section X.

EPA has compounded its erroneous PoD with unfounded safety and uncertainty factors. In 2011, EPA recommended that its FQPA safety factor for chlorpyrifos be 1X due to the robust toxicology dataset in support of the registration. However, the Agency's 2016 RHHRA sets a 10X FQPA safety factor—resulting in an even lower permitted exposure level—and does so because the proposed new regulatory standard resulting from the crack and crevice scenario is considered a LOAEL (lowest observed adverse effect level) rather than a NOAEL (no observed adverse effect level). But this use of a LOAEL/NOAEL approach is totally inappropriate. Among other flaws, this approach ignores the statutory requirement that FQPA safety factors,

especially those used to revoke tolerances, must be based on valid, reliable data. *See infra*, Section VII.

In addition, EPA's decision to set a 10X intraspecies uncertainty factor is based on EPA's conclusion that the physiologically based pharmacokinetic ("PBPK") model for chlorpyrifos does not adequately address the life-stage of pregnancy. DAS has recently updated the PBPK model to account for this life-stage, and this work has been reviewed by independent scientific experts, who concluded that the changes to the model were sufficiently robust and validated to allow use by EPA and other regulatory bodies for risk assessments involving pregnant women. Accordingly, EPA should now be able to reduce the intraspecies uncertainty factor for pregnant women or women of childbearing age to 4X. *See infra*, Section IX.

Additionally, EPA's application of the FQPA Safety Factor to occupational risk assessment is inappropriate and leads to an inflated level of concern and overestimate of risk. EPA's residential post-application and bystander risk assessments also lack plausibility/reasonableness and ignore critical studies previously relied upon by the Agency. *See infra,* Section X.B.

Moreover, as set forth in detail herein, DAS is very concerned that EPA's proposed regulatory action relies on an unrefined drinking water assessment that is still based on screening-level modeling, is not adequately refined, and far over-estimates levels found in the real world. EPA's drinking water assessment ignores important, science-based refinements provided by DAS in a study submitted in February 2016 and in comments submitted to previous dockets by DAS and other experts. *See infra*, Section XI.

Finally, EPA's assessments ignore the significant economic impact of revocation of chlorpyrifos tolerances. U.S growers and farmers and the USDA have made clear the critical need for and value of this important crop protection tool in previous comments, which EPA has not acknowledged. U.S. growers, many of them small family farms, along with food processors and other distribution companies, will be severely impacted by EPA's proposed action. Global trade of key crops and crop products important to U.S. consumers will also be negatively affected. When combined, the economic impact could easily make the proposed revocation of tolerances a significant regulatory action. *See infra*, Section XII.

In sum, EPA is proposing regulatory action that is far from the "stepwise, objective, and transparent" process the Agency claims. In order to be consistent with established, good scientific methodology and rational regulatory decision-making, EPA should implement two steps immediately. First, EPA should convene an SAP(s) to review the Agency's 2016 RHHRA and drinking water assessment for chlorpyrifos. A formal request for SAP review has been submitted to the Agency by thirty-five major agricultural organizations. *See* Ex. 1. EPA has thus far asked for SAP review at every critical juncture with respect to its possible reliance on the Columbia study and other epidemiology studies to inform its decision-making. The 2016 RHHRA presents no less of an unprecedented approach to regulation, for the reasons set forth herein, and similarly demands SAP review. The court's deadline does not justify a failure to conduct thorough, science-based SAP review of EPA's unprecedented methodologies that are reflected in both the 2016 RHHRA and drinking water assessment.[6] Second, EPA should deny the Petition and postpone taking final action on chlorpyrifos until the Agency has completed Registration Review pursuant to FIFRA.

III. Regulatory History and Robust Toxicology Data Affirm that the Current Regulatory Standard for Chlorpyrifos Protects Human Health.

EPA sets exposure limits and bases its human health risk assessments for chemicals based on conservative and health-protective endpoints (also known as a point of departure or "PoD") that have historically been identified through required animal testing. For chlorpyrifos, inhibition of red blood cell ("RBC") cholinesterase ("ChEI") has always been (since chlorpyrifos was first registered more than forty-five years ago) the point of departure used by EPA and also

[6] In its December 21, 2016 Revised Human Health Risk Assessment for tetrachlorvinphos ("TCVP RHHRA"), EPA announced that it would be opening a comment period on a petition submitted by CropLife America asking the agency to "halt regulatory decisions that are highly influenced/determined by results of epidemiological studies that do not meet well-defined data quality standards, and that are not integrated into the health risk assessment in a transparent, well-defined manner." EPA said it would open this comment period based on its determination that any final action for TCVP "could potentially be impacted by EPA consideration of the epidemiological studies identified in the [CropLife] petition." TCVP RHHRA at 13. Because EPA's proposed revocation for chlorpyrifos is similarly based on epidemiological studies that do not meet well-defined data quality standards and that have not been integrated into EPA's risk assessment in a transparent manner, no decision should be made on chlorpyrifos until this review by EPA is complete.

remains the gold standard and point of departure used by the World Health Organization[7] and virtually all major global regulatory authorities. Numerous SAPs convened specifically by EPA over the last eight years have confirmed ChEI as the appropriate PoD for chlorpyrifos.

In a radical departure in 2016, however, EPA proposed to set the PoD for chlorpyrifos on cord blood levels in humans (the Columbia study) that are claimed to be associated with a non-specific and as yet unidentified and unvalidated effect and for which EPA has never received or reviewed the actual raw data. The most recent (2016) SAP rejected EPA's attempt to abandon the use of RBC ChEI in favor of using cord blood as the PoD from the Columbia study cohort. EPA's departure in approach after forty-five years is seemingly based on an abrupt change in regulatory policy, as there is no new science that would merit moving away from a conservative and health-protective endpoint that is used globally by all other regulatory authorities.

A. There is a Long and Well-Supported Regulatory History of Using Cholinesterase Inhibition as the Biological Endpoint Upon Which Risk Assessment for Chlorpyrifos is Based.

As noted earlier, acetylcholinesterase ("AChE") inhibition ("AChEI") is the mode/mechanism of action for effects of chlorpyrifos to the mammalian system. EPA regulates on a particular type of AChE which is Red Blood Cell Acetylcholinesterase ("RBC AChE") inhibition, or simply Red Blood Cell cholinesterase inhibition ("RBC ChEI").

To provide a succinct history of the Agency's consistent use of RBC ChEI as the point of departure, the following is provided beginning in 2000, although cholinesterase inhibition has always been used by EPA in its risk assessments for chlorpyrifos. In 2000, during its reregistration review for chlorpyrifos, EPA stated that "[i]nhibition of ChE is the most sensitive effect in all animal species evaluated and in humans, regardless of route or duration of exposure." EPA, Human Health Risk Assessment – Chlorpyrifos, at 2 (June 8, 2000). For risk assessment during the 2000 reregistration review, EPA used a combination of plasma, RBC, and brain ChEI from a variety of laboratory animal studies.

[7] The World Health Organization ("WHO") has completed multiple evaluations of chlorpyrifos toxicology and human safety since 1972. The WHO has consistently recognized acetylcholinesterase inhibition as the most sensitive toxicological effect of chlorpyrifos in mammals and established recommended risk assessment endpoints for human health protection based on acetylcholinesterase inhibition.

In 2008, EPA reaffirmed the use of ChEI as the appropriate PoD for chlorpyrifos specifically, stating that "[c]hlorpyrifos, like other organophosphates, binds to and phosphorylates the enzyme acetylcholinesterase (AChE) in both the central (brain) and peripheral nervous systems (USEPA, 1999), leading to accumulation of acetylcholine and, ultimately, to clinical signs of toxicity. This mode of action, in which AChE inhibition leads to neurotoxicity, has been well described (Mileson et al. 1999)." EPA, App. B – Mode of Action: Inhibition of Acetylcholinesterase (AChE), at 3 (Aug. 27, 2008). To put this reaffirmation in perspective from a timing aspect, Columbia study researchers started publishing in 2002 on exposure, and the infant outcome studies were first published in 2004. EPA was therefore aware of the Columbia study results when they reaffirmed ChEI as the appropriate PoD.

In its Science Issue Paper: Chlorpyrifos Hazard and Dose Response Characterization (USEPA, 2008), EPA stated that "[b]lood ChE inhibition was used as the endpoint for all scenarios." EPA, Science Issue Paper: Chlorpyrifos Hazard and Dose Response Characterization, at 9 (Aug. 21, 2008). This decision was confirmed by a FIFRA Scientific Advisory Panel (2008), which reviewed EPA's Issue Paper and stated that "cholinesterase inhibition should continue to be used for PoD until, at such time, an alternative mode of action is identified and validated." EPA, 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, at 12 (Dec.17, 2008) ("2008 SAP Minutes"). No such alternative mode of action has been identified or confirmed to the present day. It is also important that this SAP concluded that "[t]he Panel agreed that the epidemiological studies have utility for risk assessment, but not as the principal basis for characterization of the point of departure (PoD)." *Id.* at 10.

In 2009, EPA issued its Revised Human Health Assessment Scoping Document in Support of Registration Review and again noted that "[i]nhibition of ChE was the most sensitive effect in all animal species evaluated." EPA, Chlorpyrifos. Revised Human Health Assessment Scoping Document in Support of Registration Review, EPA-HQ-OPP-2008-0850-0003, at 2 (Feb. 9, 2009). In the Scoping Document, EPA stated that "[t]he scoping team concluded that the only new toxicology data needed at this time to support the registration review of chlorpyrifos is an immunotoxicity study and an acute and repeated comparative cholinesterase assay (CCA) study." *Id.* There was no indication at this time, nor any new data to suggest that

investigations in animals were needed to explore possible other modes of action or to determine if effects were occurring below 10% RBC ChEI.

In 2011, in its Chlorpyrifos: Preliminary Human Health Risk Assessment for Registration Review, EPA affirmed that "[t]he toxicology database for chlorpyrifos is substantially complete (40 CFR 158.340 guideline studies have been submitted) and has been used to characterize toxicity and for selecting points of departure for purposes of the current risk assessment." EPA, Chlorpyrifos Preliminary Human Health Risk Assessment for Registration Review ("PHHRA"), at 7 (June 30, 2011). Further, the Agency said that it "is maintaining, at this time based on available data, that cholinesterase inhibition (ChEI) provides the most sensitive dose-response information for deriving points of departure for chlorpyrifos. In animals, significant inhibition of plasma and red blood cell (RBC) ChE occur at doses below those that cause brain ChE inhibition." *Id.*

EPA convened a Scientific Advisory Panel in 2012 to review the available animal toxicological data for chlorpyrifos. In its first question (Question 1), EPA again reaffirmed cholinesterase inhibition as the primary mode of action and stated "AChE data remain the most robust dose-response data for deriving points of departure" and asked the SAP to confirm:

> *EPA Question 1.0:*
>
> It is well established that AChE inhibition is the primary mode of action/adverse outcome pathway for OPs, like chlorpyrifos. Because AChE inhibition is the initiating event for this mode of action/adverse outcome pathway, using AChE inhibition as a regulatory endpoint is protective of downstream cholinergic effects. Moreover, historically, given the sensitivity of AChE inhibition data for OPs, these data have been considered to be protective of other potential toxicities and/or modes of action for OPs. In 2008, the Agency performed a comprehensive review of the available AChE data from multiple lifestages. This review has been supplemented with the newest studies. Consistent with the recommendations from the 2008 SAP, the Agency believes that AChE data remain the most robust dose-response data for deriving points of departure in *in vivo* experimental toxicology studies with laboratory animals. *Please comment on the Agency's preliminary conclusion that AChE data remain the most robust source of data for deriving points of departure for chlorpyrifos. Please include a discussion of the strengths and uncertainties of this preliminary conclusion.*

EPA, Transmittal of Meeting Minutes of the FIFRA Scientific Advisory Panel Meeting held April 10–12, 2012 on "Chlorpyrifos Health Effects" ("2012 SAP Minutes") at 12 (July 11, 2012). The 2012 SAP Panel Response notes that all studies reporting neurobehavioral effects

following exposures have shown AChEI also occurred. Again, this SAP was convened after the Columbia study published articles were initially available:

> The Panel concurs with the Agency's position that AChE data continue to be the strongest resource of data for deriving points of departure for chlorpyrifos. The Panel's conclusion is based on the premise that all studies reporting neurobehavioral changes following *in vivo* prenatal or postnatal exposures to chlorpyrifos have been accompanied by AChE inhibition when measured at an appropriate time following administration of chlorpyrifos.

Id. The Panel also weighed in on studies that purport to demonstrate neurodevelopmental effects either below 10% RBC ChEI or through a non-cholinergic mode of action and concluded that:

> [S]tudies evaluating neurodevelopmental effects entailed experimental designs that do not permit an efficient means of determining a point of departure for chlorpyrifos. Thus, just as in the 2008 SAP, this Panel advises that the Agency continue to use AChE data at the most sensitive lifestages for dose-response analysis and deriving points of departure. Also in keeping with the 2008 SAP, this Panel expresses concern about the use of Dimethyl Sulfoxide (DMSO) as a vehicle because of its intrinsic toxicity, its potential influence on absorption and interaction with chlorpyrifos, and the impact of this interaction on the developing organism.

Id. In 2014, upon release of the Chlorpyrifos: Revised Human Health Risk Assessment for Registration Review, EPA employed a PBPK model for chlorpyrifos in determining a PoD. *See* EPA, Chlorpyrifos: Revised Human Health Risk Assessment for Registration Review (Dec. 29, 2014) ("2014 RHHRA"). EPA continued, however, to propose 10% inhibition of RBC ChEI as its regulatory standard. Use of the PBPK model also allowed the reduction of the interspecies (animal to human) extrapolation factor and intraspecies (across humans) extrapolation factor for the general population.

As recently as late 2015, in its Proposed Rule, EPA affirmed its confidence in its current regulatory standard, stating that "AChE inhibition remains the most robust quantitative dose response data for chlorpyrifos and thus continues to be the critical effect for the quantitative risk assessment." Proposed Rule, Fed. Reg. at 69,087. The Agency observed that this approach is consistent with advice of the 2008 and 2012 SAPs, which were specifically charged with evaluating the Agency's approach to evaluating the toxicity of chlorpyrifos. *Id.*

But then EPA made a radical shift in proposing to change the "PoDs from doses eliciting 10% RBC . . . AChE inhibition to adverse effects changes in neurodevelopment as measured by

epidemiology studies conducted by [the Columbia study]." 2016 SAP Minutes at 10. In effect, what EPA did was abandon its long-standing position (and multiple SAP recommendations) that cholinesterase inhibition represents the most sensitive and robust endpoint for risk assessment and move abruptly to what EPA described as "the conceptual approach to using the cord blood data to derive PoDs for women of childbearing age, . . . infants, and children." EPA, Chlorpyrifos Issue Paper: Evaluation of Biomonitoring Data from Epidemiology Studies, EPA-HQ-OPP-2016-0062-0005 at 11 (Mar. 11, 2016) ("Chlorpyrifos Issue Paper"). However, EPA's proposal was not based on new information, but rather a 2011 publication of the Columbia study, in which the study authors reported decrements in Working Memory, an index of the IQ test. The fact that this move in 2016 was based on information that was available some five years earlier and before the various reviews cited above suggests EPA's current proposal is based on a dramatic shift in regulatory policy rather than science. This move also signified that EPA was going to abandon its reliance on animal toxicology data, the standard that has been in place since chlorpyrifos was first registered in the United States.

Following release of its proposal, EPA convened yet another SAP (2016) on its proposed approach to using cord blood from the Columbia study as the PoD. The Panel stated that:

> The majority of the Panel did not agree with the Agency's use of the results from a single longitudinal study to make a decision based on the use of cord blood measures of chlorpyrifos as a PoD for risk assessment. . . . The majority of the Panel stated that using cord blood chlorpyrifos concentrations for derivation of the PoD could not be justified by any sound scientific evaluation.

2016 SAP Minutes at 18–19.

Despite the SAP's strong recommendation to *not* use the Columbia study data for derivation of a PoD, *see* 2016 RHHRA at 3 ("The 2016 SAP did not support using the cord blood quantitatively for deriving PoDs."), the Agency, in November of 2016, released the current RHHRA. In this revised assessment, the Agency has departed even more from standard and long-standing risk assessment approaches by assuming an exposure (gathered from phone conversations with former crack and crevice applicators; no actual data used) to pregnant women who gave birth to children from the Columbia study and for which there is a purported, yet undefined neurodevelopmental effect associated with those children.

B. EFSA Review of Epidemiology Studies Confirms that the Current Regulatory Standard is Appropriate.

A recent reevaluation of chlorpyrifos-related toxicology and selection of regulatory endpoints for human health was completed by the EFSA on behalf of the European Commission (EFSA, 2014). Chlorpyrifos had been included in Annex I (list of approved active substances) to Directive 91/414/EEC during 2006 as part of the EU Review process. In 2012, a data call-in for submission of new studies completed since the time of the EU Review was issued, and these new studies were first evaluated by Spain, the rapporteur member state, and subsequently subjected to peer review under the auspices of EFSA. The result of the EFSA peer review was that "[t]he experts agreed on the use of the Red Blood Cell cholinesterase inhibition to derive the reference values." EFSA J. 2014; 12(4):3640 at 2. This represented a change in approach in that, previously, endpoints for chlorpyrifos and other organophosphorus insecticides had been established based on brain cholinesterase inhibition and/or observation of cholinergic symptoms. Accordingly, EFSA took its recommendations for further peer review by its Panel on Plant Protection Products and their Residues ("PPR Panel") during 2014. The PPR Panel endorsed the proposed acetylcholinesterase-based Acceptable Daily Intake, Acute Reference Dose, and Acceptable Operator Exposure Level proposed by EFSA. This action thus aligned the endpoint with the RBC ChE inhibition endpoint previously used by EPA, but not the dramatically lower endpoint currently proposed by EPA in the 2016 RHHRA.

As part of the European Commission reevaluation of chlorpyrifos toxicology and human health (EFSA, 2014), EFSA paid particular attention to the results of studies, including those being cited by EPA (Lovasi et al. 2011; Rauh et al. 2012; Rauh et al. 2011; Rauh et al. 2006; Whyatt et al. 2009; Whyatt et al. 2007; Whyatt et al. 2004), the Mount Sinai Hospital Children's Environmental Health Cohort (Berkowitz et al. 2004; Engel et al. 2007; Engel et al. 2011) (the "Mt. Sinai study"); and the UC Berkeley's Center for the Health Assessment of Mothers and Children of Salinas (CHAMACOS) Cohort (Bouchard et al. 2011; Eskenazi et al. 2004; Eskenazi et al. 2010; Eskenazi et al. 2007; Harley et al. 2011; Marks et al. 2010; Young et al. 2005) (the "CHAMACOS study"). The EFSA peer review made the following conclusion regarding these studies:

> The epidemiology data are not sufficiently robust to support the hypothesis that CPF is a causal factor for neurodevelopmental effects. Exposures in the epidemiology studies are at least 1000-fold lower than those used in the animal

> studies, but the animal toxicity data do not provide clear evidence that CPF is associated with neurodevelopmental effects at doses that are below the threshold for inhibition of AChE in the brain…. Although multiple mechanisms have been proposed to explain the neurodevelopmental effects of chlorpyrifos, a coherent mode of action with supportable key events, particularly with regard to dose-response and temporal concordance, has not been elucidated yet.

EFSA. (2014). Final addendum to the Art. 21 Review on chlorpyrifos – public version – Initial risk assessment provided by the Rapporteur Member State Spain for the existing substance CHLORPYRIFOS as referred to in Article 21 of regulation (EC) No. 1107/2009. February, 2014. Chapter: Add. III to Vol. 3, Ch. 6 to DAR. Pg. 53-54. University researchers (Ntzani et al. 2013), under contract with EFSA reviewed the epidemiology studies published since 2006. They concluded there is no evidence to suggest an association between pesticide exposure, including chlorpyrifos, and neurodevelopmental effects. As previously described, EFSA (2014) also supported the use of RBC ChE as the most appropriate endpoint for assessing health risks from chlorpyrifos, and concluded the epidemiology data are not sufficiently robust to support a causal relationship with neurodevelopment effects.

* * *

In sum, over the course of the Registration Review for chlorpyrifos since 2008, EPA has moved from a consistent, long-standing, and conservative approach (and one that is used globally by regulatory authorities) of using RBC ChEI based on a complete toxicological database to an approach that is based on speculative exposure data and an undefined effect in children based on one epidemiological study for which EPA has never received nor reviewed the raw data. DAS has previously commented on both RBC ChEI as the conservative PoD as well as the limitations of the Columbia study for use in risk assessment, but to date, EPA has not provided any response to those comments.

References:

EFSA. (2014). Final addendum to the Art. 21 Review on chlorpyrifos – public version – Initial risk assessment provided by the Rapporteur Member State Spain for the existing substance CHLORPYRIFOS as referred to in Article 21 of regulation (EC) No. 1107/2009. February, 2014. Chapter: Add. III to Vol. 3, Ch. 6 to DAR. Pg. 53-54.

Mileson, B.E., Chambers, J.E., Chen, W.L. et al. 1998. Common Mechanism of Toxicity: A Case Study of Organophosphorus Pesticides. Tox. 41:8-20.

Ntzani EE, Chondrogiorgi M, Ntritsos G, Evangelou E,Tzoulaki,I. (2013). Literature review on epidemiology studies linking exposure to pesticides and health effects. EFSA supporting publication 2013: EN-497. 159 pp.

EPA, Transmittal of Meeting Minutes of the FIFRA Scientific Advisory Panel Meeting held April 10–12, 2012 on "Chlorpyrifos Health Effects" (July 11, 2012).

EPA, Human Health Risk Assessment – Chlorpyrifos (June 8, 2000)

EPA, Science Issue Paper: Chlorpyrifos Hazard and Dose Response Characterization (Aug. 21, 2008).

EPA, App. B – Mode of Action: Inhibition of Acetylcholinesterase (AChE) (Aug. 27, 2008).

EPA, Chlorpyrifos: Revised Human Health Assessment Scoping Document in Support of Registration Review, EPA-HQ-OPP-2008-0850-0003 (Feb. 9, 2009).

EPA, Chlorpyrifos: Preliminary Human Health Risk Assessment for Registration Review (June 30, 2011).

EPA, Chlorpyrifos: Revised Human Health Risk Assessment for Registration Review. (Dec. 29, 2014).

EPA, Chlorpyrifos Issue Paper: Evaluation of Biomonitoring Data from Epidemiology Studies, EPA-HQ-OPP-2016-0062-0005 (Mar. 11, 2016).

EPA, Transmittal of Meeting Minutes of the April 19–21, 2016 FIFRA SAP Meeting Held to Consider and Review Scientific Issues Associated with "Chlorpyrifos Analysis of Biomonitoring Data" (July 20, 2016).

EPA, Chlorpyrifos Revised Human Health Risk Assessment for Registration Review (Nov. 3, 2016).

IV. The 2016 SAP, USDA, and Other Experts Have Consistently Challenged EPA's Unprecedented Attempt to Set a New Regulatory Standard for Chlorpyrifos on the Basis of the Columbia Study.

EPA sought guidance from the April 2016 SAP on its proposal to set a new regulatory standard on the basis of the Columbia study. The Panel raised numerous and significant concerns with EPA's use of the Columbia study to inform regulatory action, in particular the use of a single cord blood measurement to estimate exposure and the lack of biological plausibility for a causal link between chlorpyrifos and health effects at the extremely low levels reported in the Columbia study, among others. *See, e.g.,* 2016 SAP Minutes at 22–23. The Panel also expressed concerns with the lack of raw data; the lack of validation and replication of study

results; the absence of practices to ensure the credibility of the research; and questionable approaches in the analyses of the information reported in the published articles about the study. *Id.* at 41, SAP Tr. at 89. The SAP's concerns are consistent with those of other scientific and regulatory experts, USDA, and several prior SAPs.

A. The 2016 SAP Did Not Agree with EPA's Proposal to Rely on the Columbia Study, Given its Deficiencies and Limitations, and Concluded that Cord Blood Measurements at Birth Were an Insufficient Basis to Establish a Point of Departure.

The SAP strongly discouraged EPA from setting a new PoD for chlorpyrifos based on reported cord blood information from the Columbia study. The Panel considered "the Agency's use of the results from a single longitudinal study to make a decision with immense ramifications based on the use of cord blood measures of chlorpyrifos as a PoD for risk assessment [to be] premature and possibly inappropriate." 2016 SAP Minutes at 25. The SAP was unequivocal in its assessment that EPA's proposal was contrary to proper scientific methodology: "[t]he reliance on a single cord blood measurement from only one study, *i.e.*, the Columbia study, as the primary basis for a highly impactful regulatory decision, appears to go against standard practices of science in the field of toxicology and pharmacology." SAP Tr. at 537–38.

Moreover, many Panel members expressed their concern about the validity of the cord blood results. *See, e.g.,* SAP Tr. at 89 ("I disagree with the validity of the cord blood data, really."); *id.* at 501 ("But you know, I personally don't really think that cord blood is usable as an exposure assessment for anyone here, really."). Panel members further criticized the lack of replication of study results; the fact that Good Laboratory Practices ("GLPs") were not in place to ensure the credibility of the research; and, questionable approaches in the analyses of the data. 2016 SAP Minutes at 22–23. The Panel also questioned the underlying biological plausibility of a causal link between chlorpyrifos at levels reported in the Columbia study and the health effects reported, noting the Panel is not aware of any scientific evidence where pg/g levels in the blood would lead to deleterious neurotoxicological effects in a mammalian system. *Id.* at 23. And while EPA argued at the 2016 SAP that the validity of the Columbia study should be accepted, even without access to the raw data, since the research papers had been peer-reviewed by the publishing journals, the Panel concluded such review of research studies cannot be equated to studies designed under GLP or Clinical Laboratory Improvement Amendments ("CLIA")

standards, especially when measurements and conclusions have not been independently replicated. *Id.* at 41.

The 2016 SAP members also challenged EPA's proposal to use a 2% reduction in Working Memory as the benchmark health effect for setting a PoD. Panel members raised serious concerns regarding the lack of biological plausibility for how low cord blood (low parts per trillion) concentrations of chlorpyrifos can alter Working Memory and produce neurodevelopmental impairment, and concluded that the Agency provided insufficient justification to utilize this methodology. SAP Tr. at 536 ("Without any evidence in the animal literature or elsewhere of this mechanism of action, that could explain how pg/g levels in the blood could impair IQ and/or Working Memory there does not appear to be a biological plausibility.").

The numerous concerns raised by the SAP seriously undermine the Agency's reliance on cord blood to establish a point of departure. Most importantly for purposes of EPA's 2016 RHHRA, because the SAP has concluded that the cord blood test results reported in the Columbia study's published findings are invalid and unreliable (and without the raw data to properly assess the reliability and validity of the study's findings) any conclusions reached based on the study's findings are, by extension, inherently unreliable and cannot form the basis for regulatory action. This is particularly true as to a regulatory action with ramifications as significant and far-reaching as tolerance revocation.

B. The 2016 SAP, Other Experts, and Another Federal Agency Have Identified Numerous Additional Deficiencies in the Columbia Study for Purposes of Risk Assessment.

Beyond EPA's improper reliance on the Columbia study's published cord blood results, the SAP, USDA, and other experts have raised a host of very significant concerns about any effort by the Agency to rely on the Columbia study for purposes of regulatory decision-making. For example, the SAP's deep concern regarding the absence of the raw data for the Columbia study transcends the cord blood issue and goes to the heart of any reliance on the study for regulatory purposes:

> [I]t's been said several times, having data would help people draw their own conclusions, including the agency, on how to proceed. . . . *[N]ot having data was just amazing, flabbergasting. What's going on?* . . . In order for a registrant to put a new pesticide on the market or to re-register a pesticide the data has to be very

> vigorous. Now we're looking at something the opposite. . . . So if we're basing this on one study where it's not been reproduced, you can't get the actual hard data, there's lots and lots of points below levels of detection, one has to give that really serious thought.

Id. at 494, 766 (emphasis added).

The SAP also expressed significant concerns about other aspects of the Columbia study, including the lack of replication, reliance on one study for such a critical regulatory decision, and the absence of generalizability:

- "Now I know you're on a deadline, but again, given the national and possibl[e] international ramifications of such a point of departure one would at least like to see replication." SAP Tr. at 627;

- "I don't believe epidemiology alone should drive the decision of such magnitude like this. . . . [T]here's not enough evidence to change the current [point of departure] guidelines." *Id*. at 769;

- "I'm concerned about . . . using one epi study for risk assessment. That really gives me a lot of pause. . . . [U]sing one study does set sort of a bad precedent." *Id.* at 771–72.

- "I disagree with the validity of the cord blood data, really." *Id.* at 89;

- "[The Columbia Study] is plagued by issues that diminish the enthusiasm for this study and create a host of uncertainties." *Id.* at 622;

- "I would feel uncomfortable trying to make regulations or policy [based on the Columbia Study] because I don't think the data are very strong." *Id.* at 768.

In connection with the 2016 SAP, other scientific and regulatory experts also noted numerous deficiencies with the Columbia study. For example:

> [t]he published articles [for the Columbia study] fail to account for iron deficiency and the paternal IQ, and the medical records assessment (*e.g.*, Apgar scores, maternal medication) and analysis are not explained. In addition, the articles fail to account for socioeconomic stressors, including alcohol and drug use and violence, which have been proven to have a direct impact on neurodevelopmental outcomes. Consequential exposure to other toxins such as lead and other non-organophosphate chemicals may also be important, but are not adequately addressed. Perhaps most concerning, however, is the published articles' failure to accurately account for gestational age . . . as a confounding variable. New lines of research have demonstrated that gestational age has a significant effect on neurodevelopmental outcomes. The difference of even one week in a baby's age at birth can lead to adverse neurodevelopmental effects, including lower scores on

> the Bayley scales of mental and motor development. This research has led to changes in obstetrical practices during the time of the Columbia Study.

Dr. Banner Comments at 5–6, EPA-HQ-OPP-2016-0119 (Apr. 18, 2016) ("Dr. Banner Comments") (citations omitted).[8] In addition, these experts echoed the SAP's concerns regarding use of the study for regulatory purposes in the absence of the raw data. *See, e.g.,* Decl. of Dr. Rita Schoeny In Supp. of Br. of *Amici Curiae* CropLife America ¶ 21, *PANNA v. EPA*, No. 14-72794 (9th Cir. July 5, 2016), ECF No. 40-12 ("Regardless of the regulatory standard EPA ultimately adopts, the absence of the raw data underlying the Columbia Study and a thorough analysis of that raw data present key scientific vulnerabilities to the Agency's assessment for chlorpyrifos."), Ex. 2; Dr. Banner Comments at 4, Ex. 3 ("It is troubling and inexplicable to me that the Columbia Study investigators have not made the raw data underlying this taxpayer-funded research publicly available, and even more so that EPA is emphasizing the importance of the Study in guiding its regulatory action in the absence of the raw data. Details of the Study methods and raw data allow for the replication and understanding of scientific studies. Providing the data for scientific evaluation and peer-review is an integral part of the scientific process and is a standard practice in many disciplines. It is especially crucial with complex databases where multiple methods of analysis may be employed and the final results may not completely reflect all of the methods in use."). EPA has not even acknowledged, let alone addressed, these deficiencies in its 2016 RHHRA.

Following the 2016 SAP report, DAS convened a panel consisting of former senior government officials and independent expert consultants with extensive scientific and regulatory experience to address several charge questions related to EPA's regulatory action with respect to chlorpyrifos (the "Expert Panel" or "Panel"). Specifically, the Panel was asked to provide its scientific opinion regarding EPA's proposed use of the Columbia study in the current chlorpyrifos human health risk assessment. The Panel included members with expertise in epidemiology, FQPA statutory language and interpretation, exposure assessment, reproductive and developmental toxicology, regulatory risk assessment, and dose response assessment. The

[8] Dr. Banner's Comments, which are attached as Exhibit 3 and incorporated herein, raised numerous additional limitations and deficiencies in the Columbia Study.

Panel identified numerous concerns with the Columbia study and expressed its strong disapproval of the use of the study for regulatory decision-making:

> The Expert Panel notes that specific issues that limit the quality, validity, completeness, and reliability of the [Columbia] data were described in this Report, by OPP's Scientific Advisory Panel, by other scientists in a previous report submitted to the Agency (Goodman et al. 2016) and/or by other agencies. The extent and degree of concordance in assessment of these issues is striking. Further, the issues raised are not minor, but, in fact, are fundamental to the development of robust and credible data that can withstand scrutiny. Issues that have been found to be highly problematic for the [Columbia] studies include:
>
> - The studies lack longitudinally-designed analyses with repeated exposure and outcome (and if needed, confounder) measures.
> - The studies do not include exposure assessments taking into account relevant timing (e.g., multiple sampling points) as well as consideration of method sensitivity, biomarker specificity and stability, matrix adjustment considerations, and sample contamination.
> - The study analyses may have inadequately controlled for important confounders.
> - The studies do not include sensitivity analyses including formal assessment of bias that address the inherent uncertainty of observational research.
> - There is evidence that the reported associations lack within-study consistency and are in disagreement with findings from other studies.
>
> **Recommendation:** The Expert Panel recommends that *OPP not rely on the [Columbia] cohort study as the basis for its chlorpyrifos risk assessment as the data do not meet the criteria of quality, validity, completeness, and reliability*.

Food Quality Protection Act (FQPA) Expert Panel Report, at 11 (Oct. 17, 2016), Ex. 4 (emphasis added).

USDA has also called into question EPA's reliance on the Columbia study in regulatory decision-making, asserting that EPA's decision to base "application of an additional FQPA safety factor on epidemiological evidence appears to be a novel application." USDA Public Comments on the Chlorpyrifos, Tolerance Revocations, a Proposed Rule published in the Federal Register on Nov. 6, 2015; EPA docket EPA-HQ-OPP-2015-0653 at 4, EPA-HQ-OPP-2015-0653-0369 (Jan. 5, 2016). USDA also requested "that the data underlying the foundational epidemiologic studies supporting EPA's human health risk assessment for chlorpyrifos be procured by EPA and released for expert peer review." *Id.* at 5. Finally, USDA noted numerous deficiencies in the methodology of the epidemiological studies relied on by EPA (including the

Columbia study), such as whether the study adequately considered other confounding factors and employed appropriate statistical techniques. *Id.* at 6.

C. The 2016 SAP's Conclusions About the Columbia Study Are Consistent with Three Prior SAPs.

EPA has convened several SAPs to provide guidance on issues relating to the epidemiologic research studying chlorpyrifos. All three SAPs identified shortcomings and other concerns with the Columbia study that EPA has failed to adequately address or even consider. *See also* DAS Response to EPA's 2014 RHHRA at 11, Dow AgroSciences LLC's Response to EPA Revised Human Health Risk Assessment for Chlorpyrifos Registration Review, EPA-HQ-OPP-2008-0850-0845 at 35.

1. Limitations Raised by the 2008 SAP and in EPA's 2011 PHHRA

In September 2008, EPA convened an SAP to provide a preliminary review of experimental toxicology and epidemiology data available at that time, including the Columbia, Mt. Sinai, and CHAMACOS studies. The SAP found that "it cannot be stated that chlorpyrifos is the sole contributor to the observed outcomes" and due to the limitations in the studies, discouraged EPA from using the studies quantitatively in risk assessment. EPA, Transmittal of Meeting Minutes of the FIFRA Scientific Advisory Panel Meeting Held September 16–18 on the Agency's Evaluation of the Toxicity Profile of Chlorpyrifos (the "2008 SAP Minutes") at 13, 37.

In its 2011 PHHRA, EPA considered these three federally funded epidemiology studies, as well as the 2008 SAP review of them, and identified numerous limitations with the studies. PHHRA at 29–34. In particular, EPA discussed the SAP's findings that the Columbia study subjects were exposed to multiple chemicals and other OPs. PHHRA at 32. EPA also observed that the Columbia study subjects "are from low income multi-ethnic populations and urban neighborhoods and may experience other exposures that may also influence neurodevelopmental outcomes." PHHRA at 33. EPA acknowledged the 2008 SAP's recommendation that epidemiology studies not be considered quantitatively for deriving PoDs. PHHRA at 33. EPA concluded in its PHHRA that it would "carefully consider the strengths and limitations of the epidemiology studies *along with the available empirical data* in a full weight of evidence analysis in the final [human health risk] assessment." PHHRA at 34 (emphasis added).

2. Limitations Raised in 2012 SAP

In April 2012, EPA convened another SAP to review the Agency's preliminary conclusions regarding a "weight-of-evidence" approach to integrating epidemiologic research with the experimental toxicology studies for the neurodevelopmental outcomes and AChE inhibition. The 2012 SAP also identified several weaknesses and other concerns with respect to the epidemiologic research, including the Columbia study. In particular, the panel found that it was "very difficult" to attribute the effects observed to a single chemical, given that the subjects were exposed to multiple chemicals over a multi-year period and given the complexities in a child's brain maturation process. 2012 SAP Minutes at 17, 45 ("[I]t cannot be stated that chlorpyrifos is the sole contributor to the observed outcomes."); *Id.* at 42 (cautioning against "identifying any one specific chemical as the main one associated with the cognitive deficits observed at 7 years of age in the Columbia cohort.") The panel also raised concern about "the modest sample sizes of the studies," which it deemed "one of the most important limitations of these studies [including the Columbia study]." 2012 SAP Minutes at 17–18.

The 2012 SAP further observed that the epidemiology studies, including the Columbia study, were insufficient to derive a PoD. The panel recognized "the limitations of estimating chlorpyrifos exposures based on the exposure measures collected in [the Columbia study, the Mt. Sinai study, and the CHAMACOS study]" and thus "concur[red] with EPA that the data generated from these studies alone [were] *not adequate enough to obtain a point of departure (POD) for the purposes of quantitative risk assessment*." *Id.* at 19 (emphasis added); *see also id.* at 50 ("[T]he use by the three studies of different exposure matrices . . . and different targeted analytes . . . [made] the effort of deriving a definitive POD based on those data alone impossible."). Importantly, the panel found that the three epidemiology studies under consideration, including the Columbia study, "were primarily focused on assessing health outcomes associated with a variety of environmental factors, and *were not designed to conduct a quantitative exposure assessment for chlorpyrifos*." *Id.* (emphasis added).

3. Limitations Raised in 2012 Federal Peer Review

In 2012 EPA sought input from scientists within the federal government regarding a 2012 published article describing the results of magnetic resonance imaging on a subset of the children in the Columbia study (the "2012 Federal Peer Review"). The 2012 Federal Peer Review also

discussed several limitations and other concerns with the Columbia study, including the small sample size and use of a general IQ measure to quantify cognition:

> The results [of Rauh et al. (2012)] must be interpreted very cautiously since there were only 6 males in the high exposure group and 9 in the low exposure group . . . . The study only used a general IQ measure to quantify cognition in this study and more specific cognitive and behavioral tests would be needed to pinpoint specific cognitive processes affected by CPF exposure.

Comments from Dr. Freund to EPA Aug. 3, 2013 Request for Peer Review at 1–2. The Federal Peer Review also questioned the generalizability of the findings, highlighting the "need for future research with larger samples and other populations." Comments from Dr. Bitsko to EPA Aug. 15, 2012 Request for Peer Review at 1; *see also* Comments from Dr. Chelonis at 2 (observing that "given that the sample of children used in the Rauh et al. studies had very different characteristics than that of the samples on which these [psychological] measures were standardized, observing that caution should be used when describing the results, *especially when attempting to generalize these findings to the general population*") (emphasis added). Finally, the Federal Peer Review considered the possibility that lead could have impacted the study's findings, because "there is evidence that even low levels of lead can impact neurodevelopment, and even that the observed neurobehavioral deficits are more pronounced at lower blood lead levels when compared with higher blood lead levels." Comments from Dr. Bitsko to EPA, July 23, 2012 Request for Peer Review at 1–2 (citations omitted) (emphasis added). While it had been "reported that lead was not associated with chlorpyrifos; however, given the sample size, *this may not be a reliable finding*." *Id.* (emphasis added).

* * *

Clear from the foregoing comments from multiple SAPs and other experts is that the Columbia study is simply not sufficiently robust to be used in regulatory decision-making. *See, e.g.*, Declaration of Jennifer Seed in Supp. of Br. of *Amici Curiae* CropLife America, ¶ 24, *PANNA v. EPA*, No. 14-72794 (9th Cir. July 5, 2016), ECF No. 40-11, Ex. 5 ("Because of the numerous limitations with the Columbia study that have been identified by several SAPs and other sources, it is not clear to me that there will ever be a rational, science-based justification for EPA to use the Columbia study as a basis for a new regulatory standard for chlorpyrifos or otherwise rely on it for its regulatory decision-making for chlorpyrifos until such time that the

findings are confirmed in other populations, including adequate blood sampling at appropriate timepoints for chlorpyrifos.").

V. EPA is Relying on a Flawed Assumption Concerning any Demonstrated Link Between Noncholinergic Effects and Chlorpyrifos Exposures at Ultra Low Concentrations.

As justification for its precedent-setting approach for the risk assessment of chlorpyrifos because of concerns over neurodevelopmental effects that might occur below an exposure level associated with 10% RBC ChEI, EPA claims that animal studies increasingly show effects below this threshold. Neither EPA nor the SAP Minutes, however, provide credible citations pointing to such evidence. In addition, there is no new science that demonstrates effects from toxicological studies below a threshold of 10% RBC ChEI. Perhaps most importantly, there *does* exist GLP-compliant and EPA-required research conducted by the registrant on chlorpyrifos that demonstrates no effects below a threshold of 10% RBC ChEI, but EPA fails to recognize or cite this research. Moreover, the few studies that EPA references as supportive of effects below 10% RBC ChEI have significant experimental challenges that both EPA and the SAP have recognized but are currently ignoring. EPA has not provided, and SAPs have confirmed, that there is no known toxicological mode of action that would be associated with effects below a threshold of 10% RBC ChEI and as such, no animal model that would support the contention that epidemiological studies associate exposure to chlorpyrifos with neurodevelopmental outcomes below a threshold of 10% RBC ChEI. Finally, regarding human epidemiological evidence, the suggestion that there is evidence for adverse health outcomes associated with chlorpyrifos exposures below levels that result in 10% RBC ChEI is not a demonstration of causation. The mere suggestion of an association should not form the basis for a precedent-setting regulatory action and warrants further rigorous study

A. EPA Fails to Provide Credible Evidence Demonstrating Adverse Health Outcomes in Animal Studies with Chlorpyrifos Exposures Below a Threshold Associated with 10% RBC ChEI.

1. The SAP Did Not Confirm or Fully Support that Toxicological Studies Support Effects Below 10% RBC ChEI.

In its current 2016 RHHRA, the Agency states that 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,

which was used as the POD in the EPA's 2014 RHHRA and for the 2015 proposed revocation rule." 2016 RHHRA at 3. DAS is concerned that while EPA is contending that the Columbia study purports to show an association between chlorpyrifos exposure below a level corresponding to less than 10% RBC ChEI and neurodevelopmental effects, there is now the additional suggestion that toxicology studies also suggest effects below 10% RBC ChEI. There is, however, no credible scientific evidence to support this contention. Neither the recent 2016 SAP nor EPA's 2016 RHHRA provide a single scientific citation to support this contention.

In addition, a more complete review of the SAP minutes demonstrates that the 2016 SAP made several qualifying statements that undermine EPA's position that the toxicological database supports its newly proposed action. In particular, the SAP minutes state as follows:

> There is an accumulating body of animal and in vitro evidence to suggest that organophosphates affect a variety of biological targets in addition to acetylcholinesterase (AChE). A few of these studies suggest that these targets may even be affected at levels that are below the threshold of AChE inhibition. *However, to our knowledge, very little of this evidence would (so far) suggest that blood levels of chlorpyrifos in the pg/g range would have significant deleterious neurotoxicological effects in a mammalian species. Without any evidence in the animal literature or elsewhere of a mechanism of action that could explain how pg/g levels in blood could impair IQ and/or working memory, there does not appear to be biological plausibility*.

2016 SAP Minutes at 40–41 (emphasis added). Moreover, the 2016 SAP pointed out that effects at these extremely low levels are rarely seen even with the most potent acetylcholinesterase-inhibiting drugs, further challenging the plausibility of EPA's conclusions. *See* 2016 SAP Minutes at 54 ("There is a lack of biological plausibility or animal evidence for how picomolar (pM; 10-12M) cord blood levels of >6.17 pg/g chlorpyrifos (>17.6 pM based on the CCCEH analytical results) can alter working memory and produce neurodevelopmental impairment. The mechanisms for how such potent effects can be produced at these concentrations in vivo are not known and have not been previously described. By comparison, the most potent selective anti-AChE drugs in current clinical use to treat deficits in working memory are known to directly engage brain AChE with inhibitory constants (IC50's) in the range of 20,000 pM (physostigmine) to 600,000 pM (tacrine). In this regard, CPFO, the active metabolite of chlorpyrifos, has an IC50 towards AChE of ~10,000 pM. One is left to speculate on one or more causative mechanisms having potencies more than 1,000-30,000 fold lower than cholinergic

drugs known to alter working memory in patients. These estimates are conservative, since they assume chlorpyrifos levels in cord blood will directly reflect CPFO levels in the developing brain, an assumption that is currently unproven given the challenges in directly measuring the active metabolite CPFO in any tissue after exposure."). Moreover, even assuming there were evidence of effects at below levels that result in 10% RBC ChEI, the more complete citation from the SAP Meeting Minutes shows that the SAP strongly discouraged the application of additional uncertainty factors to account for possible effects at levels below 10% of RBC ChEI: "*[T]the Panel agrees with the Agency that applying additional safety factors to the AChE PoDs to account for a possible noncholinergic mode of action (MOA) would be problematic because of challenges in justifying any particular value for such an adjustment*." *Id.* at 18 (emphasis added).

2. EPA-Required Studies Demonstrate Protectiveness of Cholinesterase Inhibition and No Neurodevelopmental Effects Below Exposures Associated With 10% RBC ChEI.

DAS, as primary registrant of chlorpyrifos, has conducted guideline and GLP-compliant studies that demonstrate that the use of cholinesterase inhibition is health protective and that there are *no neurodevelopmental effects at levels below exposures associated with 10% RBC ChEI*. In the landmark neurodevelopmental study (Maurissen et al. 2000), for example, dams were administered 0.3, 1, or 5 mg/kg/day. Even the lowest dose level administered (0.3 mg/kg/day) resulted in substantial plasma and RBC ChEI, but notably there were no effects on learning or memory in pups at either the 0.3 or 1 mg/kg/day level. This study thus supports the long-held view that ChEI remains a sensitive and protective endpoint for risk assessment.

In addition, to specifically comply with an EPA data requirement and in order to purposely explore low dose effects related to chlorpyrifos exposure, another study (Marty et al. 2012) was conducted for chlorpyrifos. During the repeated dosing part of the study, pups and dams were administered chlorpyrifos at levels of 0, 0.05, 0.1, 0.5, 1.0, and 3.5 mg/kg/day. The lower end of the dose range in this study is substantially lower than those testing regimes in the vast majority of other studies cited by EPA. Results of this study showed that there were no effects on neurobehavior as evaluated through a functional observation battery and motor activity evaluation in the repeat portion of the study in either dams or pups at dose levels that were associated with less than 10% RBC ChEI in both female pups (0.1 mg/kg/day) and dams (0.05

mg/kg/day). Male pups also had no effects associated with functional observation battery or motor activity, but had approximately 14% RBC ChEI at the lowest dose (0.05 mg/kg/day) tested. This study thus provides an example of where neurodevelopmental effects were not observed in in vivo testing at exposures associated with approximately 10% RBC ChEI or lower.

Finally, a review of both EPA and SAP publications and reviews during Registration Review of chlorpyrifos demonstrate that there is little, if any, data from toxicological studies showing that neurodevelopmental effects result from exposure to chlorpyrifos that results in less than 10% RBC ChEI. A complete summary of these publications and reviews is set forth in Appendix D, Summary of Former EPA and SAP Reviews of Robustness of Animal Toxicology Literature for Chlorpyrifos Relative to Existing Regulatory Standard. *See also* Section III, *supra* (summarizing how the regulatory history and toxicology data for chlorpyrifos affirm that the current regulatory standard protects human health).

In summary, EPA is taking unfounded liberties in inferring that there is evidence for adverse health outcomes in toxicology studies associated with chlorpyrifos exposures below levels that result in 10% RBC ChEI.

References:

EPA, Transmittal of Meeting Minutes of the April 19-21, 2016 FIFRA SAP Meeting Held to Consider and Review Scientific Issues Associated with "Chlorpyrifos:Analysis of Biomonitoring Data" (July 20, 2016).

Johnson, F.O., Chambers, J.E., Nail, C.A., et al. 2009. Developmental chlorpyrifos and methyl parathion exposure alters radial-arm maze performance in juvenile and adult rats. Tox. Sci. 109:132-142.

Marty, M.S., Andrus, A.K., Bell, M.P., et al. 2012. Cholinesterase inhibition and toxicokinetics in immature and adult rats after acute or repeated exposures to chlorpyrifos or chlorpyrifos-oxon. Reg Toxicol. Pharmacol. 63:209-224.

Maurissen, J.P.J., Hoberman, A.M., Garman, R.H., et al. 2000. Lack of selective developmental neurotoxicity in rat pups from dams treated by gavage with chlorpyrifos. Tox. Sci. 57:250-263.

EPA, Transmittal of Meeting Minutes of the FIFRA Scientific Advisory Panel Meeting held April 10–12, 2012 on Chlorpyrifos Health Effects (July 11, 2012).

EPA, Science Issue Paper: Chlorpyrifos Hazard and Dose Response Characterization (Aug. 21, 2008).

EPA, Chlorpyrifos: Preliminary Human Health Risk Assessment for Registration Review (June 30, 2011).

EPA, Chlorpyrifos: Revised Human Health Risk Assessment for Registration Review (Dec. 29, 2014).

EPA, Chlorpyrifos: Revised Human Health Risk Assessment for Registration Review (Nov. 3, 2016).

B. The 2016 SAP's Statement that "[E]pidemiology . . . studies *suggest there is evidence* for adverse health outcomes associated with chlorpyrifos exposures below levels that result in 10% RBC AChE inhibition" Does Not Demonstrate Causation.

In its 2016 RHHRA, EPA repeatedly refers to the 2016 SAP's statement that "epidemiology . . . studies *suggest there is evidence* for adverse health outcomes associated with chlorpyrifos exposures below levels that result in 10% RBC AChE inhibition." 2016 RHHRA at 18, 25, 53. EPA implies that this statement is validation for cause and effect between exposure to chlorpyrifos and the neurodevelopmental effects observed in the Columbia cohort, and justifies the Agency's crack and crevice methodology and time weighted average approach. But the Agency has grossly inflated the significance of the SAP's statement. First, it is well-settled that "[e]pidemiology does not measure causation, only association." Dr. Banner Comments at 5. *See also* Dow AgroSciences LLC's Response to EPA Revised Human Health Risk Assessment for Chlorpyrifos Registration Review, EPA-HQ-OPP-2008-0850-0845 at 35 (Apr. 29, 2015) (noting that case law and EPA's own DRAFT Framework for Incorporating Human Epidemiologic & Incident Data in Health Risk Assessment have observed that epidemiology studies suffer from deficiencies and do not prove causation). The 2016 SAP was not charged with determining causation, and EPA is simply wrong to rely on the SAP's statement for proof of causation.

Second, EPA takes the SAP's actual statement out of its proper context. EPA fails to note that this statement was made as part of a discussion regarding the numerous concerns the SAP had about using the Columbia study quantitatively for risk assessment purposes. SAP Tr. at 622 ("[O]ther panel members have an opinion that the [Columbia] study, while suggesting a link between prenatal chlorpyrifos exposure and developmental impairments, *is plagued by issues that diminish the enthusiasm for this study and create a host of uncertainties*. The panel agrees that . . . epidemiology . . . studies *suggest* there is . . . evidence for adverse health outcomes

associated with chlorpyrifos exposures below levels that result in 10 percent red blood cell acetylcholinesterase inhibition. However, the panel agrees with the agency that applying additional safety factors to acetylcholinesterase PoD to account for a possible noncholinergic [mode of action] would be problematic because of the challenges in justifying any particular value for such adjustment." (emphasis added)). The context within which the quoted statement was made makes it clear that the SAP did not find a validated causal connection between chlorpyrifos exposures below 10% RBC AChE inhibition and adverse health outcomes. In addition, the SAP's phrases "suggest there is evidence" and "associated with" do not describe causation, and do not mean "definitively shows" or "demonstrates." Indeed, the SAP did not make a causal determination between cord blood measures and neurodevelopmental outcomes. SAP Tr. at 623 ("In other words, cord blood measures of chlorpyrifos *may be associated* with neurodevelopmental outcomes *but not causal*.") (emphasis added). A mere "suggestion" of an "association" implies that further study is warranted and is simply not enough on which to base major, precedent-setting regulatory action.

VI. EPA's Proposed Regulatory Point of Departure for Chlorpyrifos is Based on a Dose Reconstruction Methodology that is Scientifically Flawed, Contrary to the Weight of the Evidence and SAP Recommendations, and for which Scientific Peer Review is Absent, and Violates Due Process.

Ignoring the Columbia study's limitations and the guidance of numerous SAPs, EPA is now advancing a new, theoretical exposure assessment that rests on the Agency's flawed assumption that the Columbia study establishes a causal relationship between chlorpyrifos exposure and neurodevelopmental impacts. EPA is advancing this approach based on the Columbia study findings notwithstanding the 2016 SAP's conclusions that the cord blood data underpinning those findings are unreliable and invalid. In addition, EPA's exposure assessment is based on unsupported and hearsay assumptions about chlorpyrifos use. Specifically, the input values used by the Agency to calculate the PoD were calculated based on an assumed crack and crevice exposure scenario that did not take into account exposure from other routes such as diet or drinking water.

Moreover, contrary to the Agency's suggestion, EPA's new proposal for assessing exposure does not comport with the 2016 SAP's recommendations. It is also contrary to the scientific weight of the evidence, including other epidemiologic research, and the Agency's own recommendation for the integration of epidemiology in risk assessment, as set forth in its 2010

Draft Framework for Incorporating Human Epidemiologic & Incident Data in Health Risk Assessment. EPA, Draft Framework for Incorporating Human Epidemiologic & Incident Data in Health Risk Assessment (Jan. 7, 2010) ("Draft Framework").

EPA's new exposure assessment is especially problematic because its methodologies and conclusions have not been subjected to independent peer review. As explained above, EPA is proposing to take unprecedented regulatory action on the basis of significant changes in established scientific methods for setting a PoD. In addition to the need for further review of the scientific validity of the Agency's continued reliance on the results from the Columbia study, EPA's proposed approach to setting a new PoD contains several other significant issues that have not been validated or addressed in previous SAPs. EPA's 2016 RHHRA presents yet another unprecedented approach based in significant part on the Columbia study, and as set forth in the request to EPA Administrator Gina McCarthy submitted by thirty-five U.S. agricultural organizations (dated January 12, 2017), the proposed approach demands additional, independent SAP review. *See* Ex. 1.

A. EPA Continues to Improperly Make the Columbia Study the Centerpiece for its Latest Regulatory Approach.

As explained in Section IV.A., above, the 2016 SAP roundly rejected EPA's unprecedented proposal to derive a new PoD for chlorpyrifos based on as yet unseen biomonitoring data from the Columbia study. Panel members uniformly disagreed with basing regulatory action on a single, unreplicated study. *See, e.g.,* SAP Tr. at 534–38, 771–72 (reliance on one study goes "against standard practices of science "and sets a bad precedent"). In addition, Panel members raised concerns about EPA's reliance on a single measure of chlorpyrifos in cord blood to develop a new regulatory standard. The Panel's concerns were consistent with those of several prior SAPs, which deemed the Columbia study insufficient for use quantitatively in risk assessment. *See supra,* Section IV.C.

Rather than address the SAP's recommendations in a scientifically rational way, EPA has instead developed yet another (and even more questionable, non-validated) regulatory proposal in a last ditch effort to salvage the Columbia study as the basis for undermining decades of rigorous toxicology data that support existing health assessments of chlorpyrifos around the world. To be sure, the "scientific evidence" underlying EPA's latest proposal has not changed. EPA has simply developed a new, fictitious exposure assessment in an attempt to sidestep the

SAP's concerns about using a single cord blood measurement quantitatively to derive a PoD. Though EPA claims to be using the Columbia study "qualitatively," *see* 2016 RHHRA at 14, EPA's new analysis is premised on its scientifically unsupported assumption that the Columbia study findings establish a *causal* linkage between neurodevelopmental outcomes and chlorpyrifos exposures below the current regulatory level. *See* 2016 RHHRA at 13 ("EPA's assessment is that the [Columbia study] . . . provides sufficient evidence that there are neurodevelopmental effects occurring at chlorpyrifos exposure levels below that required for AChE inhibition."); *see also* J. Dawson, *Alternative Risk Assessment Approach In the U.S. - Chlorpyrifos*, 4th Fresenius Worker Exposure and Risk Assessment Conference, Mainz Germany, at 14, 15 (Dec. 1, 2016) ("Dawson Presentation") (describing first step in EPA's new "hybrid" approach to determine a PoD as "[c]alculate internal dose *causing* neurodevelopmental effects") (emphasis added). With that assumption in place, the Agency proceeds through dose reconstruction to "calculate" the level of exposure that theoretically must have occurred to the Columbia study cohort to produce the effects purportedly observed.

EPA's exposure assessment, however, rests on ill-conceived assumptions about chlorpyrifos use and thus does not meet the level of scientific rigor required for use in tolerance revocation. *See* FFDCA § 408(b)(2)(D)(i), 21 U.S.C. § 346a(b)(2)(D)(i) (EPA must consider "the validity, completeness, and reliability of the available data from studies of the pesticide" in revoking tolerances). In addition, by resting its dose reconstruction analysis on the fundamental assumption that there is a causal link between chlorpyrifos exposure and neurodevelopmental effects (the so-called "qualitative findings"), EPA is accepting the validity of the Columbia study's published findings (which are based on the heavily criticized methodology using the as yet unseen cord blood data) and thus continues to make improper *quantitative* use of the Columbia study.

Finally, EPA's revised analysis completely glosses over additional noted deficiencies in the Columbia study. In the 2016 RHHRA, EPA acknowledges various "uncertainties" in the epidemiologic research, including "the lack of an established MOA/AOP pathway, the inability to make strong causal linkages, and the unknown window(s) of susceptibility" but goes on to state that "[t]hese uncertainties do not undermine or reduce the confidence in the findings of the

epidemiology studies."[9] 2016 RHHRA at 12. In fact, several prior SAPs have reached the very opposite conclusion, determining that numerous and significant limitations in the study made it inappropriate for use in quantitative risk assessment. *See supra*, Section IV.C

B. EPA's Dose Reconstruction Analysis Rests on Unsupported and Hearsay Assumptions about Chlorpyrifos Use.

To develop a new PoD for risk assessment from internal concentrations of chlorpyrifos, EPA reviewed the registered uses that would have been available to the Columbia study cohort. 2016 RHHRA at 14. EPA then conducted interviews with technical pest advisors responsible for overseeing New York City's housing authority and "determined" that crack and crevice use was the predominant type of application method used at the time of the Columbia Study nearly two decades ago. *Id.* at 14–15. Using methodology from EPA's Standard Operating Procedures (2012 Residential SOPs) for that type of application, EPA estimated a theoretical time-weighted average ("TWA") exposure. Using PBPK modeling not peer reviewed for this particular unprecedented use, EPA then estimated an equivalent internal dose. As set forth below, there are a number of critical issues undermining the credibility of EPA's exposure assessment. For further detailed discussion by Driver, et al. 2017 and the expert examination of the dose reconstruction by CLA see comments submitted to the docket.

1. There is no definitive evidence that crack and crevice applications of chlorpyrifos took place.

The 2016 RHHRA states:

> [I]n 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 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 [schedule of cancelled uses of other chlorpyrifos residential use products],

[9] This is but one of numerous examples of EPA's unprecedented and tortured use of the term "uncertainties" when it comes to chlorpyrifos. For purposes of EPA risk assessment, "uncertainty" was not intended to be used for a situation in which biological plausibility and causation, for example, cannot be established. Reliance on a study in such a situation represents nothing more than guesswork or, at best, hypothesis generation and the need for further research. Nor is the term "uncertainty" appropriate where the Agency has failed to obtain the raw data underlying a study in order to assess the credibility and replicability of the study. These situations instead amount to deficiencies, weaknesses and flaws in the study and/or the use of the study, seriously limiting or negating its use for purposes of risk assessment.

> the agency has focused on crack and crevice exposures for the 2016 risk assessment.

2016 RHHRA at 15. Thus, EPA is basing its unprecedented regulatory action on the recollection of private pesticide applicators and technical advisors responsible for pest control in New York City's housing authority nearly two decades ago to determine the most likely exposure method.

In fact, only three people from two organizations were interviewed, and the Record of Correspondence lacks transparency because it does not publish the specific questions asked of the applicators. *See* EPA Record of Correspondence, EPA-HQ-OPP-2015-0653-0439. The two employees of Assured Environments, a privately owned pest control company in New York, were asked about the typical residential application method for chlorpyrifos in New York City during the time period from 1997 to 2000. But the Record does not indicate whether the interviewer first established whether chlorpyrifos was regularly used or whether other active ingredients were applied alone or in rotation with chlorpyrifos. Indeed, a review of the Columbia study publications demonstrates that crack and crevice use was not representative of the exposure scenarios reported in the Columbia study. *See, e.g.,* Whyatt, et al., Residential Pesticide Use during Pregnancy among a Cohort of Urban Minority Women (2002) at 510 (observing that sticky traps were the most common method used by a sample of 231 women from the Columbia study); Whyatt, et al., A Biomarker Validation Study of Prenatal Chlorpyrifos Exposure within an Inner-City Cohort during Pregnancy (2009) at 562 (stating that 32% of Columbia Study subjects "reported using baits, gels, and traps only," and that 29% of that sample "reported using one or more of the spray methods (can sprays, sprays by exterminator, and pest bombs) with or without the other methods"). In a second interview, of a former Technical Advisor for Pest Control for the New York City Housing Authority, EPA noted that an integrated pest management approach was employed; this included caulking and rotating chemistries so that not just chlorpyrifos was used. Retreatment occurred after three to four months if necessary.

In addition, EPA's evidence gathering constitutes blatant hearsay and raises a number of fact issues: How accurate is the recollection of the pest advisors? Did they actually work in the buildings occupied by the Columbia cohort and, if so, how often during the relevant period? If not, how can they confirm that crack and crevice was in use in the buildings occupied by the Columbia cohort? What additional information did the pest advisors tell EPA not reported in EPA's summary interview memorandum? In short, it is deeply troubling to DAS that these

tenuous, opaque findings based on *recall* of practices taking place sixteen to nineteen years ago form the basis of the Agency's unprecedented use of crack and crevice application as the exposure scenario for dose reconstruction.

2. Even worst-case estimates of crack and crevice exposure represent a small fraction of total aggregate sources of exposure that the Columbia cohort (and the U.S. population) experienced.

In deriving the PoD, EPA assumed that the primary exposure to the Columbia study cohort was via the dermal route as the result of post-application exposure to possible crack and crevice applications of chlorpyrifos and that it was this exposure that caused the claimed effects. An examination of National Health and Nutrition Examination Survey ("NHANES") biomonitoring data for the same period, however, indicates that the greatest potential exposure to chlorpyrifos was through dietary intake and not through other routes such as post-application exposure following crack and crevice treatment. *See* Driver et al. 2017 for analysis. In fact, the NHANES data supports the conclusion that crack and crevice use constituted approximately 20% of the dose derived from dietary and water sources. To consider post-application exposure to crack and crevice application of chlorpyrifos in isolation is not consistent with the aggregate exposure to dietary and food sources that are even greater than crack and crevice exposures and that occurred on a daily basis (and not on a geometrically reduced level each day as EPA assumed for post-application crack and crevice exposure). *See also* Driver et al. 2017. To then assume that the exposure to chlorpyrifos from the crack and crevice treatment was the cause of these effects, when even those who did not have the applications had basically the same exposures, is not scientifically supported.

3. There are many deficiencies associated with EPA's modeling of crack and crevice exposure.

While DAS agrees that the 2012 Standard Operating Procedures for Residential Exposure ("SOPs") provide the appropriate method to calculate crack and crevice exposure, and agrees that PBPK modeling can be used to provide estimates of daily blood levels from crack and crevice application, the specific crack and crevice scenario exposure estimation methodology employed by the 2016 RHHRA raises questions regarding accuracy, precision, representativeness, and reliability, specifically in the context of deriving a PoD.

Several of EPA's SOP inputs seem to be arbitrary; the appropriateness and reliability of these assumptions are discussed fully by Driver et al. and by CLA. These inputs include the

assumption of 10% dissipation of surface residues per day for chlorpyrifos, which may be exaggerated; the assumption that pregnant women spent two hours per day every day on hard surfaces involving extensive and intense dermal contact; all women were assumed to take a shower daily immediately following contact with the hard surface over a thirty-day interval; and EPA only considered inhalation exposure for a two-hour period and dermal exposures for the remaining thirty days. No other exposures were included (*e.g.*, dietary intake as mentioned above), resulting in a gross under-estimate of internal dose. EPA's assumptions likely underestimated actual exposures and therefore resulted in a PoD that is likely unrealistically low.

4. EPA's PoD is not supported by biomonitoring data.

The 2016 SAP members observed that PBPK modeling "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." 2016 Minutes at 18. Despite the availability of multiple studies conducted using biomonitoring following crack and crevice application, and also biomonitoring data available from NHANES (which is concordant with EPA's DEEM dietary exposure modeling for the general population), there have been no valid biomonitoring data cited by EPA for the purpose of comparison with the crack and crevice exposure estimate or the PBPK model results. Such comparison would be accepted practice for validation of the modeling.

There are several studies in which biomonitoring was conducted following crack and crevice application; these have been reviewed by Driver et al. 2017. The studies analyzed 3,5,6-trichloropyridinol (TCPy), a metabolite of chlorpyrifos, in the urine of study participants. In order to determine the contribution that post-application exposure has on TCPy concentration in urine it is important to measure the TCPy concentration before crack and crevice exposure to establish the background concentration in urine. The background concentration can then be subtracted from the post-application concentration in urine to calculate the TCPy that is attributed to the crack and crevice post-application exposure. In these biomonitoring studies a crack and crevice internal dose of 0.002 – 0.09 μg/kg/day was reported (Table 1) which is consistent with EPA's calculated dose for just crack and crevice exposure (0.0077 μg/kg/day for first 24 hr or an average of 0.0027 μg/kg/day over thirty days; *see* Driver et al. 2017 for further details). However, and this is a key point, the pre-exposure (background) monitoring values and the total daily exposure (*i.e.*, crack and crevice exposure plus background) in the same volunteers were 100-fold greater than the Agency-calculated values for crack and crevice alone. The

majority of the TCPy measured in urine is likely resulting from exposures from food, which shows that the Agency body burden estimates based on crack and crevice exposure is not realistic. Dose reconstruction should be an aggregate across all routes and potential pathways/sources (food, water, indoor residential and other product uses including public health vector control, etc.).

Table VI.1. Comparison of Crack and Crevice ("C&C") Dose Estimates (extracted from Driver et al. 2017)

Study	**Pre-C&C Treatment (µg/kg/day)**	**C&C Treatment Only (µg/kg/day)**	**Aggregate (µg/kg/day)**	**Notes**
Agency Estimate: EPA, RHHRA 2016	NA	0.006[a]	Unknown	75 kg women
Byrne et al., 1998[b]	0.11-0.87	0.002-0.09	0.46 ± 0.30; (0.2-0.88)[c]	household
Hore et al., 2006 [b]	NA	NA	0.32	children
Hore et al., 2006[d]	0.04-1.6	<0.0-0.92	0.17-1.4	children
Krieger et al., 2001[b]	0.3-2.1	NA	0.8-5.3	household

[a]This is an estimate, using the Agency scenario and PBPK model for 10 days to be consistent with Bryne et al. and Hore et al., who monitored TCPy in urine for 10-11 days post C&C. The value reported in the text, 0.0027 µg/kg/day is over the entire 30-day exposure.
[b] These values are based on urinary elimination of TCPy.
[c] Mean +/- standard deviation; range.
[d] Averages for Days 1-5. Note on average over the first 5 days, peak aggregate is lower than pre-treatment maximum.
NA- not available

In summary, with regard to the dose construction, there is no definitive evidence that crack and crevice applications of chlorpyrifos took place, yet a recollection of practice taking place almost two decades ago forms the basis of the Agency's unprecedented use of crack and crevice application as the exposure scenario for dose reconstruction. Furthermore, even worst-case estimates of crack and crevice exposure represent a small fraction of total aggregate sources of exposure that the Columbia cohort (and the U.S. population) experienced; the aggregate exposure to dietary and food sources are even greater than crack and crevice exposures and these occurred on a daily basis (and not on a geometrically reduced level each day as EPA assumed for post-application crack and crevice exposure). Several of EPA's SOP inputs are arbitrary, and

these assumptions likely underestimated actual exposures and therefore resulted in a PoD that is unrealistically low.

References:

Driver, J., Ross, J., Poet, T., Hastings, K., Burns, C. (2017) Public Comments: Chlorpyrifos Revised Human Health Risk Assessment for Registration Review (EPA's Office of Pesticide Programs, November 3, 2016) Posted on EPA-HQ-OPP-2015-0653)

CLA 2017 Comments Regarding Calculation of the Chlorpyrifos Time Weighted Average Concentration in the Blood. Posted on EPA-HQ-OPP-2015-0653

C. EPA's Latest Methodology Actually Shows No Dose-Response Relationship Between Chlorpyrifos and Neurodevelopmental Outcomes.

Before the 2016 SAP, EPA proposed developing a PoD derived from biomonitoring data from the Columbia study. EPA relied on the Columbia study researchers' division of the study subjects into two groups based on the exposure levels derived from chlorpyrifos levels in cord blood: a "higher" exposure group (>6.17 pg/g) and a "lower" exposure group (<6.17pg.g). Chlorpyrifos Issue Paper at 12. EPA then credited the researchers' findings that there were statistically significant differences in neurodevelopmental outcomes as between the high and lower exposure groups. In other words, EPA concluded that those study subjects exposed to higher amounts of chlorpyrifos had a higher likelihood of adverse neurodevelopmental effects compared to the lower exposure group.

In its present analysis, EPA has calculated a single value (0.004 µg/L) as the TWA blood concentration for all Columbia Study subjects based on crack and crevice application. 2016 RHHRA at 17. Thus, EPA is assuming that neurodevelopmental effects purportedly associated with chlorpyrifos exposure are more likely to occur at levels above 0.004 µg/L. EPA's assessment thus concludes that study subjects received the same dose and is no longer drawing a distinction between "higher" and "lower" exposure groups. But if there is no quantitative difference in exposure between the two groups, there is no dose-response relationship and thus no plausible PoD to derive. The lack of a dose-response relationship indicates that something other than chlorpyrifos was actually responsible for the neurodevelopmental effects observed, further undermining EPA's revised risk assessment.

D. Contrary to EPA's Representation, Its Latest Approach is Not Consistent with the 2016 SAP Recommendations.

EPA states in the 2016 RHHRA that its new proposal is based on the recommendations of the 2016 SAP. In particular, EPA states:

> [T]he 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. . . . [T]he 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.

2016 RHHRA at 14 (emphasis added). EPA described this approach as a "hybrid" approach.

EPA's statements about purported SAP support for its new proposal are misleading and inaccurate. The SAP suggested some areas for further analysis and approaches EPA might consider after further investigation, but did not lay down a recipe it was advising the Agency to follow. Indeed, when compared against the SAP members' actual statements during Panel deliberations, it is plain that EPA took liberties with the SAP's recommendations and took a number of their conclusions out of context. For example, during the SAP meeting, with respect to the issue of using a TWA, Panel member Dr. Russell Carr observed as follows:

> The idea that the responses observed, for example, the neurological effects, would be detrimental primarily by the blood level of chlorpyrifos at the time of delivery is not logically supportable. Peak or time weighted averaged concentrations during pregnancy or a portion thereof are more logically supported metrics. Such metrics could, in theory, be back calculated from the blood biomonitoring data using a valid [PBPK] model *if one has data on or can confidently make assumptions about aspects of exposure patterns[,] labor delivery, blood collections and other cofounding variables*. If such computations cannot be made with confidence, then cor[d] blood data should not serve as a basis for quantitative human health risk assessment.

SAP Tr. at 538:2–18 (emphasis added). This appears to be where EPA derived its TWA hybrid approach "recipe." However, Dr. Carr was suggesting that a TWA approach might be a more scientifically sound approach to estimating exposure *if* there were additional data or if assumptions could confidently be derived from exposure patterns, labor and delivery, *and* blood collection. Dr. Carr's recommendation thus assumes that EPA would be developing a TWA blood concentration level based on a plethora of blood-related data (beyond a single point in time measurement) *from the Columbia cohort itself*, not assumptions about chlorpyrifos exposure that

are theoretic and speculative and then applied to the cohort. EPA simply did not come close to following all of the important recommendations or cautions from the SAP.

E. EPA's Approach is Contrary to the Weight of the Evidence, and EPA's Attempt to Support the Columbia Study with Additional Epidemiology is Scientifically Unsound.

EPA's new approach, regardless of how it is characterized, continues to rely principally on a single epidemiology study, and casts aside entirely a complete database of guideline-compliant and GLP-adherent toxicological data demonstrating the safety of EPA's existing regulatory standard. EPA has made an unprecedented shift to an approach in which the benchmark health effect is not specified and for which there is no known mode of action. This is inconsistent with principles of sound science, is contrary to EPA's own draft guidance for the integration of human epidemiology studies in risk assessment, and ignores SAP recommendations. EPA's approach is also unsupported by other epidemiology studies, including newer lines of epidemiologic research not addressed in its 2016 RHHRA.

1. EPA has poorly followed its Draft Framework for integration of epidemiology in risk assessment

In 2010, EPA promulgated its Draft Framework, in which it announced its plans to use a weight of evidence ("WOE") approach to "evaluat[e] epidemiology and human incident data, such that all available data are evaluated and conclusions are made on the preponderance of the information rather than relying on any one study." Draft Framework at 7. EPA's Draft Framework further states that "in the WOE analysis, OPP will use the best available data across multiple lines of evidence and from in vitro, in vivo, and in silico data sources to describe the cascade of events from the exposure source to the ultimate health outcome." *Id.*

EPA has done just the opposite in its current approach, singling out and relying primarily on the Columbia study. EPA's 2016 RHHRA fails to incorporate or consider any of the toxicological data the Agency has relied upon since chlorpyrifos was first registered in the United States—including the toxicological data set the Agency deemed complete and robust as recently as 2014—with no explanation for its sudden departure from this integrated approach.

EPA's 2016 RHHRA is even contrary to comments on the Draft Framework that EPA made as recently as October 2016:

> [Mode of Action] ("MOA") and adverse outcome pathway ("AOP")] provide important concepts in this integrative analysis. Both a MOA and an AOP are based on the premise that an adverse effect caused by exposure to a compound can be described by a series of causally linked biological key events that result in an adverse human health or ecological outcome. One of the key components of the Agency's draft framework is the use the MOA framework /AOP concept as a tool for organizing and integrating information from different sources to inform the causal nature of links observed in both experimental and observational studies.

EPA, Draft "Framework for Incorporating Human Epidemiology & Incident Data in Health Risk Assessment," PPDC Meeting Nov. 3, 2016 – Session 7C, at 1 (Oct. 15, 2016). In EPA's current approach, however, EPA has departed from a PoD based on a known mode of action (cholinesterase inhibition) to one in which the health endpoint is not defined and the mode of action cannot be explained. EPA is simply inferring exposure through the alleged presence of *de minimis* amounts of chlorpyrifos in blood—test results heavily criticized by the 2016 SAP—and has identified no specific endpoint or adverse outcome pathway by which chlorpyrifos putatively affected exposed individuals.

2. EPA has not incorporated the 2010 SAP's recommendations regarding the Draft Framework.

The 2010 SAP charged with reviewing the Draft Framework made multiple recommendations for improvement to the Framework. The 2010 SAP recommended against relying upon epidemiologic studies with weak exposure assessment, even those using biomonitoring. When relying upon short-lived chemicals, the collection should be timed with the period of etiologic relevance. The SAP also suggested that the reviews of epidemiology data incorporate a minimum set of criteria for acceptability, determine if the analytic methods were appropriate, quantify the effects of bias, and include null findings in the assessment. Specifically, the 2010 SAP recommended as follows:

- "For the hypothesis-testing designs, the paramount requirement in environmental epidemiology is a well characterized, quantitative exposure assessment that minimizes exposure measurement error and decreases the likelihood of introducing misclassification in categorical or continuous data analyses. The exposure assessment should be evaluated for accuracy, precision and reliability and should include validation where feasible." EPA, Transmittal of Meeting Minutes of the FIFRA Scientific Advisory Panel Meeting [held February 2–4, 2010] 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" ("SAP 2010 minutes") at 9 (Apr. 22, 2010).

- "In the interests of transparency, the Panel recommends that the Agency establish a set of criteria for determining the acceptability of epidemiologic studies." *Id.* at 10.

- "Determine whether the assumptions of longitudinal analytic approaches are actually met and that these analytic approaches are used appropriately." *Id.* at 19.

- "[I]t is equally important to stress the need for exposure information sufficient to characterize the time period when the exposure would be likely to have its effect on the outcome of interest. In other words, the timing of exposure may be equally if not more important than the level or duration of exposure.… 'Direct' approaches, such as biomonitoring and personal monitoring, are generally not useful for characterizing prior exposures unless the contaminants of interest are very persistent (*i.e.*, bioaccumulate, long half-lives of excretion)." *Id.* at 22.

- "Methods for assessing the impacts of exposure misclassification bias, selection bias, and confounding bias exist. Inclusion of these in relevant studies should be encouraged." *Id.* at 25.

- "Studies demonstrating no association with a pesticide exposure are equally as informative in WOE analysis as those that do." *Id.* at 32.

Despite these suggestions for more robust and transparent review, EPA continues to rely upon the results of the Columbia study as evidence of neurodevelopmental effects from extremely low chlorpyrifos exposure, without a set of criteria in place for evaluation of the study for risk assessment purposes. Indeed, even the most recent SAP questioned EPA's reliance on epidemiology studies without having in place a scheme for the systematic evaluation of the strength of different studies. *See* SAP Tr. at 767. EPA justifies its reliance on the Columbia study by maintaining that the Columbia study is more robust than other studies because the parent compound was measured in blood rather than the metabolite in urine. However, the *medium* alone is not a sufficient measure of quality or reliability. The timing of collection, the biological half-life, documentation of sample stability, avoidance of sample contamination, and repeated samples are well-established aspects of quality exposure assessment. (LaKind et al. 2014).

3. The hypotheses generated by the Columbia study are not supported by other studies, in particular, the Mt. Sinai and CHAMACOS cohorts.

EPA improperly suggests that the Mt. Sinai and CHAMACOS Studies provide additional support for its new proposal for chlorpyrifos. In particular, EPA's 2016 RHHRA states that "the

agency continues to conclude that the 3 U.S. cohort studies (Columbia, CHAMACOS, and Mt. Sinai) provide the most robust available epidemiological evidence." 2016 RHHRA at 12. The CHAMACOS and Mt. Sinai studies, however, assessed non-specific organophosphate metabolites in maternal urine and did not examine chlorpyrifos specifically. PHHRA at 31.

In addition, multiple published reviews of epidemiologic findings of Columbia, Mt. Sinai, and CHAMACOS describe the evidence as inadequate, inconsistent, and implausible (Eaton et al. 2008; Li et al. 2012; Mink et al. 2012; Needham 2005; Weselak et al. 2007; Zhao et al. 2005). Similarly, the authors of a hypothesis-based weight of evidence analysis of chlorpyrifos concluded that the epidemiologic data were inconsistent between chlorpyrifos exposure and neurodevelopmental toxicity (Prueitt et al. 2011). In an unempirical manner, EPA has selected only adverse associations as evidence of causality but has not equally considered the entire scope (*i.e.*, the negative results) of the available data. When using epidemiologic data for human health risk assessment, null findings cannot be viewed as less important than positive ones. Taken together, the results of these birth cohort studies are conflicting and contradictory and do not implicate chlorpyrifos as a developmental toxicant.

4. EPA has not clearly specified the health outcome that it considered for the point of departure, and the health effects reported in the epidemiology studies are not consistent.

The 2016 SAP members challenged EPA's proposal to use a 2% reduction in working memory as the benchmark health effect for setting a PoD. Panel members raised serious concerns regarding the lack of biological plausibility for how extremely low cord blood concentrations of chlorpyrifos (low parts per trillion) can alter working memory and produce neurodevelopmental impairment, and concluded that the Agency provided insufficient justification to base the PoD upon the cord blood concentrations. EPA has now moved away from reduction in working memory and the benchmark effect is not defined at all. No SAP has ever considered such an approach.

Defining a specific adverse outcome for specific dose level is the hallmark of regulatory risk assessment. Thus, the lack of an age-specific benchmark effect is problematic. In humans, there are multiple neurodevelopmental outcomes and diagnoses from birth to age seven. Some have been evaluated by the investigators from Columbia University, Mt. Sinai, CHAMACOS and others for exposure to chlorpyrifos and/or organophosphate metabolites. However, there is

little cohesiveness across these studies with respect to using the same diagnostic criteria and evaluating the children at the same ages. Further, as mentioned above, the results across studies are not consistent. Even within the Columbia study, the results are not consistent. For example, no statistically significant associations were observed for chlorpyrifos for the Columbia study children at ages one and two, and the outcomes were not evaluated using longitudinal analytic approaches (as recommended by the 2010 SAP). At age three, the reported associations in the Columbia study analyses were stronger for the Bayley Psychomotor Developmental Index than for the Mental Developmental Index, suggesting that the focus should be upon physical, not mental, development. This is inconsistent with the initial EPA proposal to use the IQ Working Memory index (age seven) as the PoD.

5. Newly referenced epidemiology studies do not support neurodevelopment effects from chlorpyrifos exposure *in utero*.

EPA's 2016 RHHRA states:

> [T]he EPA's assessment is that the CCCEH [Columbia] 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.

2016 RHHRA at 13.

Findings from newly published studies are both negative and positive and do not contribute sufficiently to the evidence of chlorpyrifos induced neurodevelopmental effects (Bouchard et al. 2010; Fortenberry et al. 2014; Furlong et al. 2014; Guodong et al. 2012; Oulhote and Bouchard 2013; Shelton et al. 2014; Zhang et al. 2014). EPA also failed to acknowledge two other birth cohort studies in three publications (Donauer et al. 2016; Yolton et al. 2013; Cartier et al. 2016) that do *not* support adverse neurodevelopmental outcomes associated with chlorpyrifos exposure. The additional studies are summarized in Table VI.2.

Three of the new studies collected urine postnatally. The findings of these studies that rely upon exposures measured in children should be discussed in the context of other studies of postnatal exposures, such as that of Eskenazi et al. (2007) and Bouchard et al. (2011). Overall, the results of the studies of chlorpyrifos metabolites in children have not suggested an adverse effect. Two of the three studies cited by EPA found no association with urinary DEP (diethyl phosphate, a metabolite of chlorpyrifos and other organophosphates) and health outcomes

studied (Bouchard et al. 2010; Guodong et al. 2012; Oulhote et al. 2013). The CHAMACOS children with higher DEP levels tended to score higher on Bayley and IQ tests (Eskenazi et al. 2007; Bouchard et al. 2011).

Regardless of the findings, positive or negative, the studies newly introduced by EPA have a cross-sectional design. Because the exposure and outcome data were collected at the same time, the onset of disease may have preceded exposure. It is possible that observations of higher urinary concentration of a chlorpyrifos metabolite and disease can be due to behaviors unrelated to etiology but be associated to the health outcome. For example, children with behavioral problems by virtue of these problems may be more active and have greater contact with exposed surfaces and plants. Another example might be that children with well-educated and affluent parents are more likely to be diagnosed with ADHD. These parents might also provide their children a diet that is rich in fruits and vegetables, and with pesticide residues.

The other four studies do not support the Columbia Study findings. Fortenberry et al. (2014) reported no statistically significant adverse findings. Furlong et al. (2014), which is an analysis of the Mt. Sinai cohort, did not report their results for TCPy, which are assumed to also be negative. Shelton et al. (2014) used an unvalidated approach for exposure based upon residence. Zhang et al. (2014) correlated reflexes at day three with urinary DEP but did not report if these conditions were sustained as the infant developed. Consequently, and as summarized in Table VI.2, below, the epidemiology is not at all persuasive as to an association of adverse neurodevelopment due to chlorpyrifos.

a. Bouchard et al. (2010). NHANES study. Urinary DEPs in children were significantly associated with a higher prevalence of the hyperactive/impulsive subtype of ADHD. This study should be interpreted in the context of a cross sectional study of children in which the temporal sequence of exposure and outcome is unknown. **NHANES does not support or refute the Columbia in utero study findings.**
b. Guodong et al. (2012). Shanghai children. No adverse associations were reported for DEP and any developmental quotient score. This study should be interpreted in the context of a cross sectional study of children in which the temporal sequence of exposure and outcome are unknown. **The study of Shanghai children does not support or refute the Columbia in utero study finding.**

c. Oulhote and Bouchard (2013). Canada biomonitoring study. No adverse associations were reported for DEP and any developmental test. The findings are in direct conflict with those of similarly designed Bouchard et al. (2010). This study should be interpreted in the context of a cross sectional study of children in which the temporal sequence of exposure and outcome is unknown. **The Canada biomonitoring study does not support or refute the Columbia in utero study finding.**

d. Fortenberry et al. (2014). ELEMENT study. Fortenberry et al. (2014) reported no statistically significant results for urinary TCPy and any of the psychometric assessments. In the 2015 updated literature review (USEPA, 2015), EPA uses the term "suggestive" but it is unclear how this is used in the context of small sample size, poor precision and small size of the association. Specifically, the results of the ELEMENT study are misrepresented by the term "suggestive" and should be characterized as a null study and directly conflict with the ADHD findings from the Columbia study. **ELEMENT does not support the Columbia Study finding.**

e. Furlong et al. (2014). Mt. Sinai cohort. Prenatal DEP was weakly associated with reciprocal social responsiveness (RSR) among black participants and boys at age seven to nine. No statistically significant associations were found among whites or Hispanics, or among girls. Despite availability of urinary TCPy, no analyses were reported for RSR. Mt. Sinai's race and gender specific results are etiologically unsupported.

f. Zhang et al. (2014). Shenyang, China. Tested infants at three days old with the Neonatal Behavioral Neurological Assessment ("NBNA") and compared with maternal DEP concentrations prior to delivery. Decreased scores were reported and is not inconsistent with findings from CHAMACOS and Mt. Sinai. Testing of infants was not done by the Columbia Study and direct comparison cannot be made. Furthermore, the Columbia Study did not identify any statistically significant adverse results until the child was three years old., which is inconsistent with the Zhang adverse finding at infancy. No further assessment of these children has been reported. **This study does not confirm or refute the Columbia Study findings.**

g. Shelton et al. (2014). Statistically significant odds ratio ("OR") was observed for autism spectrum disorder (ASD) and residing within 1.75 km of the pesticide application (OR = 1.78). However, the ORs were smaller for living closer (OR = 1.57 and OR = 1.66 for 1.25

km and 1.5 km, respectively). Similarly, there was no dose/proximity pattern by time period of the pregnancy. Chlorpyrifos was not statistically associated with developmental delay in any analysis. The authors note that error may be introduced because they assume homogeneity of exposure within each buffer. Information on hours spent in the home or elsewhere was not available. This approach for exposure assessment fails to account for factors related to drift (application equipment, formulation, weather conditions) and presence of the subject during or after the application. **This study has unvalidated exposure assessment and should not be used to confirm or refute the Columbia study.**

Table VI.2. Summary of recent epidemiology studies.

Author, year of publication	Outcomes	Exposure Metric	Design and Discussion
Cross sectional studies (outcome and urine collected at the same time)			
Bouchard, 2010	Diagnostic Interview Schedule for Children IV	Urinary DEPs in child (-) single sample	(-) Cross sectional design Urinary DEPs in children were significantly associated with a higher prevalence of the hyperactive/impulsive subtype of ADHD
Guodong, 2012	Developmental Quotient from the Gesell Developmental Schedules	Urinary DEPs in child (-) single sample	(-) Cross sectional design No adverse associations were reported for DEP and any developmental quotient score.
Oulhote, 2013	Strengths and Difficulties Questionnaire	Urinary DEPs in child (-) single sample	(-) Cross sectional design No adverse associations were reported for DEP and any developmental test.
Case control and prospective studies			
Fortenberry, 2014	Conners' Parental Rating Scales-Revised, Conners' Continuous Performance Test, and Behavior Assessment System for Children-2	Urinary TCPy, prenatal (-) single sample 3 samples (during each trimester) for 21 of 187 participants	(+) Prospective design No statistically significant associations were observed between tertiles of maternal TCPy concentrations and ADHD-related outcomes in children ELEMENT does not support the Columbia study findings.
Furlong, 2014	Reciprocal Social Responsiveness	Urinary DEPs, prenatal (-) single sample	(+) Prospective design (Mt. Sinai cohort) Prenatal DEP associated with RSR among blacks and boys Mt. Sinai's race and gender specific results are etiologically unsupported.
Shelton, 2014	Autism Spectrum Disorder	Pesticide application near maternal residence (-) The use of residential proximity to determine exposure has not been validated	(+) Case control design with confirmed diagnosis. This study has an un-validated exposure assessment and should not be used to confirm or refute the Columbia study
Zhang, 2014	Neonatal Behavioral Neurological Assessment at 3 days	Urinary DEP, prenatal (-) single sample	(+) Prospective design Decreased scores associated with DEP. No assessment reported when child was older. This study does not confirm or refute the Columbia study findings at older ages.
Not reviewed by EPA			
Cartier, 2016	Wechsler Intelligence Scale for Children, 4th edition (WISC-IV)	Urinary DAPs, prenatal Urinary DAPs, child (-) single sample	(+) Prospective design No evidence that prenatal exposure adversely affected cognitive function in 6-year-olds.
Donauer, 2016	Bayley Scales of Infant Development Wechsler Preschool and Primary Scale of Intelligence	Urinary DAP, prenatal (+) Two samples	(+) Prospective design (HOME study) No adverse associations of gestational exposure on and cognition at 1 – 5 years of age.
Yolton, 2013	NICU Network Neurobehavioral Scale at 5 weeks	Urinary DAP, prenatal (+) Two samples	(+) Prospective design No detrimental effects of gestational exposure on neurobehavioral outcomes among young infants were reported.

(-) A weak study domain; (+) a strong study domain

References

EPA, 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 (Apr. 22, 2010).

EPA, Draft Framework for Incorporating Human Epidemiologic & Incident Data in Health Risk Assessment (Jan. 7, 2010).

EPA, Draft "Framework for Incorporating Human Epidemiologic & Incident Data in Health Risk Assessment," PPDC Meeting Nov. 3, 2016 – Session 7C, (Oct. 15, 2016).

Arnold, S.M., Morriss, A., Velovitch, J., Juberg, D., Burns, C.J., Bartels, M., Aggarwal, M., Poet, T., Hays, S., and Price, P. 2015. Derivation of human Biomonitoring Guidance Values for chlorpyrifos using a physiologically based pharmacokinetic and pharmacodynamic model of cholinesterase inhibition. Regul Toxicol Pharmacol 71(2): 235-243. doi: 10.1016/j.yrtph.2014.12.013.

Bouchard, M.F., Bellinger, D.C., Wright, R.O., and Weisskopf, M.G. 2010. Attention-deficit/hyperactivity disorder and urinary metabolites of organophosphate pesticides. Pediatrics 125(6): e1270-1277. doi: 10.1542/peds.2009-3058.

Bouchard, M.F., Chevrier, J., Harley, K.G., Kogut, K. Vedar, M., Calderon, N. Trujillo, C., Johnson, C., Bradman, A. Barr, D.B., and Eskenazi, B. 2011. Prenatal Exposure to Organophosphate Pesticides and IQ in 7-Year-Old Children. Environ Health Perspect Environ Health Perspect 119:1189–1195. doi:10.1289/ehp.1003185.

Burns, C.J., McIntosh, L.J., Mink, P.J., Jurek, A.M., and Li, A.A. 2013. Pesticide exposure and neurodevelopmental outcomes: review of the epidemiologic and animal studies. J Toxicol Environ Health B Crit Rev 16(3-4): 127-283. doi: 10.1080/10937404.2013.783383.

Cartier, C., Warembourg, C., Le Maner-Idrissi, G., Lacroix, A., Rouget, F., Monfort, C., Limon, G., Durand, G., Saint-Amour, D., Cordier, S., and Chevrier, C. 2016. Organophosphate Insecticide Metabolites in Prenatal and Childhood Urine Samples and Intelligence Scores at 6 Years of Age: Results from the Mother-Child PELAGIE Cohort (France). Environ Health Perspect 124(5): 674-680. doi: 10.1289/ehp.1409472.

Donauer, S., Altaye, M., Xu, Y., Sucharew, H. Succop, P., Calafat, A.M., Khoury, J. C., Lanphear, B., and Yolton, K. 2016. An observational study to evaluate associations between low-level gestational exposure to organophosphate pesticides and cognition during early childhood. Amer J Epidemiol 184:410-418.

Eaton, D.L., Daroff, R.B., Autrup, H., Bridges, J., Buffler, P., Costa, L.G., Coyle, J., McKhann, G., Mobley, W.C., Nadel, L., Neubert, D., Schulte-Hermann, R., and Spencer, P.S. 2008. Review of the toxicology of chlorpyrifos with an emphasis on human exposure and neurodevelopment. Crit Rev Toxicol 38 Suppl 2: 1-125. doi: 10.1080/10408440802272158.

Eskenazi, B., Marks, A. R., Bradman, A., Harley, K., Barr, D. B., Johnson, C., Morga, N., and Jewell, N. P. 2007. "Organophosphate pesticide exposure and neurodevelopment in young Mexican-American children," Environ Health Perspect (115:5) May, pp 792-798.

Farahat, F.M., Ellison, C.A., Bonner, M.R., McGarrigle, B.P., Crane, A.L., Fenske, R.A., Lasarev, M.R., Rohlman, D.S., Anger, W.K., Lein, P.J., and Olson, J.R. 2011. Biomarkers of chlorpyrifos exposure and effect in Egyptian cotton field workers. Environ Health Perspect 119(6): 801-806. doi: 10.1289/ehp.1002873.

Fortenberry, G.Z., Meeker, J.D., Sánchez, B.N., Bellinger, D., Peterson, K., Schnaas, L., Solano-González, M., Ettinger, A.S., Hernandez-Avila, M., Hu, H., and Maria Tellez-Rojo, M. 2014. Paraoxonase I polymorphisms and attention/hyperactivity in school-age children from Mexico City, Mexico. Environ Res 132: 342-349. doi: 10.1016/j.envres.2014.04.010.

Furlong, M.A., Engel, S.M., Barr, D.B., and Wolff, M.S. 2014. Prenatal exposure to organophosphate pesticides and reciprocal social behavior in childhood. Environ Int 70: 125-131. doi: 10.1016/j.envint.2014.05.011.

Garabrant, D.H., Aylward, L.L., Berent, S., Chen, Q., Timchalk, C., Burns, C.J., Hays, S.M., and Albers, J.W. 2009. Cholinesterase inhibition in chlorpyrifos workers: Characterization of biomarkers of exposure and response in relation to urinary TCPy. J Expo Sci Environ Epidemiol 19(7): 634-642. doi: 10.1038/jes.2008.51.

Guodong, D., Pei, W., Ying, T., Jun, Z., Yu, G., Xiaojin, W., Rong, S., Guoquan, W., and Xiaoming, S. 2012. Organophosphate pesticide exposure and neurodevelopment in young Shanghai children. Environ Sci Technol 46(5): 2911-2917. doi: 10.1021/es202583d.

LaKind, J.S., Sobus, J.R., Goodman, M., Barr, D.B., Fürst, P., Albertini, R.J., Arbuckle, T.E., Schoeters, G., Tan, Y.M., Teeguarden, J., Tornero-Velez, R., and Weisel, C.P. 2014. A proposal for assessing study quality: Biomonitoring, Environmental Epidemiology, and Short-lived Chemicals (BEES-C) instrument. Environ Int 73: 195-207. doi: 10.1016/j.envint.2014.07.011.

Li, A.A., Lowe, K.A., McIntosh, L.J., and Mink, P.J. 2012. Evaluation of epidemiology and animal data for risk assessment: chlorpyrifos developmental neurobehavioral outcomes. J Toxicol Environ Health B Crit Rev 15(2): 109-184. doi: 10.1080/10937404.2012.645142.
Mink, P.J., Kimmel, C.A., and Li, A.A. 2012. Potential effects of chlorpyrifos on fetal growth outcomes: implications for risk assessment. J Toxicol Environ Health B Crit Rev 15(4): 281-316. doi: 10.1080/10937404.2012.672150.

Needham, L.L. 2005. Assessing Exposure to Organophosphorus Pesticides by Biomonitoring in Epidemiologic Studies of Birth Outcomes. Environmental Health Perspectives 113(4): 494-498. doi: 10.1289/ehp.7490.

Oulhote, Y., and Bouchard, M.F. 2013. Urinary metabolites of organophosphate and pyrethroid pesticides and behavioral problems in Canadian children. Environ Health Perspect 121(11-12): 1378-1384. doi: 10.1289/ehp.1306667.

Prueitt, R.L., Goodman, J.E., Bailey, L.A., and Rhomberg, L.R. 2011. Hypothesis-based weight-of-evidence evaluation of the neurodevelopmental effects of chlorpyrifos. Crit Rev Toxicol 41(10): 822-903. doi: 10.3109/10408444.2011.616877.

Reiss, R., Chang, E.T., Richardson, R.J., and Goodman, M. 2015. A review of epidemiologic studies of low-level exposures to organophosphorus insecticides in non-occupational populations. Crit Rev Toxicol 45(7): 531-641. doi: 10.3109/10408444.2015.1043976.

Shelton, J.F., Geraghty, E.M., Tancredi, D.J., Delwiche, L.D., Schmidt, R.J., Ritz, B., Hansen, R.L., and Hertz-Picciotto, I. 2014. Neurodevelopmental disorders and prenatal residential proximity to agricultural pesticides: the CHARGE study. Environ Health Perspect 122(10): 1103-1109. doi: 10.1289/ehp.1307044.

EPA, Framework for Incorporating Human Epidemiologic & Incident Data in Health. Risk Assessment. Office of Pesticide Programs. 1-68. https://archive.epa.gov/scipoly/sap/meetings/web/pdf/020210agenda.pdf.

EPA, Chlorpyrifos; Tolerance Revocations; Proposed Rule, 80 Fed. Reg. 69,087 (Nov. 6, 2015).

Weselak, M., Arbuckle, T.E., and Foster, W. 2007. Pesticide exposures and developmental outcomes: the epidemiological evidence. J Toxicol Environ Health B Crit Rev 10(1-2): 41-80. doi: 10.1080/10937400601034571.

Yolton, K., Xu, Y., Sucharew, H., Succop, P., Altaye, M., Popelar, A., Montesano, M.A., Calafat, A.M., and Khoury, J.C. 2013. Impact of low-level gestational exposure to organophosphate pesticides on neurobehavior in early infancy: a prospective study. Environ Health 12(1): 79. doi: 10.1186/1476-069X-12-79.

Zhang, Y., Han, S., Liang, D., Shi, X., Wang, F., Liu, W., Zhang, L., Chen, L., Gu, Y., and Tian, Y. 2014. Prenatal exposure to organophosphate pesticides and neurobehavioral development of neonates: a birth cohort study in Shenyang, China. PLoS One 9(2): e88491. doi: 10.1371/journal.pone.0088491.

Zhao, Q., Gadagbui, B., and Dourson, M. 2005. Lower birth weight as a critical effect of chlorpyrifos: a comparison of human and animal data. Regul Toxicol Pharmacol 42(1): 55-63. doi: 10.1016/j.yrtph.2005.01.009.

F. EPA Must Seek Peer Review of its New, Precedent-Setting Regulatory Standard.

In addition to the numerous scientific and policy issues discussed above, EPA's RHHRA is problematic because its methodologies and conclusions have not been subjected to independent peer review. As explained above, EPA is proposing to take unprecedented regulatory action on the basis of significant changes in established scientific methods for setting a PoD. EPA is proposing a new regulatory endpoint based principally on a single, unreplicated epidemiology study—the Columbia study—for which it lacks underlying raw data. EPA is taking this action despite the concerns of no less than three prior SAPs that weaknesses and deficiencies in the Columbia study render it inappropriate for use in regulatory decision-making, and in disregard of over forty years of toxicological data demonstrating the safety of chlorpyrifos under the current regulatory standard. EPA's 2016 RHHRA presents yet another unprecedented approach based in significant part on the Columbia study and, as set forth in a request to EPA Administrator Gina McCarthy submitted by thirty-five U.S. agricultural organizations (dated January 12, 2017), *see* Exhibit 1, the proposed approach merits additional SAP review.

EPA's proposed approach to setting a new PoD contains several other significant issues that have not been validated or addressed in previous SAPs. In particular, EPA should convene an SAP to examine EPA's estimation of a theoretical TWA exposure based on questionable and hearsay assumptions about chlorpyrifos use, as well as the Agency's use of the PBPK model to estimate an equivalent internal dose from possible exposure associated with a crack and crevice application. These are novel scientific issues that no prior SAP has addressed. Indeed, EPA's sudden shift from reliance on precisely measured exposure doses in animal toxicology studies conducted under Good Laboratory Practices and required for registration, to speculative exposures determined through phone and email surveys, demands SAP review—particularly given the enormous ramifications of EPA's proposed action for U.S. agriculture.

EPA's analysis is premised on its fundamentally inaccurate assumption that, based on the Columbia study, there is a causal linkage between chlorpyrifos exposures below the current regulatory level and effects claimed in the Columbia study. But EPA's 2016 RHHRA acknowledges limitations in the Columbia study, including "the lack of established MOA/AOP pathway, *the inability to make strong causal linkages*, and the unknown window(s) of susceptibility." 2016 RHHRA at 12 (emphasis added). Indeed, no causal linkage has been established, let alone "the [ ] ability to make strong causal linkages." EPA downplays these

issues as mere "uncertainties" that "do not undermine or reduce the confidence in the findings of the epidemiology studies." *Id.* EPA's use of the Columbia study in this manner, in light of the numerous deficiencies and limitations in the study raised by prior SAPs that EPA has not addressed, warrants further independent SAP review.

In addition, proceeding with a final rule to revoke tolerances for chlorpyrifos based on the 2016 RHHRA and in the absence of external peer review would raise significant Due Process concerns. A revocation of pesticide tolerances under FFDCA is tantamount to issuance of a notice of intent to cancel the underlying registration under FIFRA Section 6. *See, e.g.*, 40 C.F.R. 152.112(g) (requiring all necessary tolerances to be issued under FFDCA § 408 as a condition of registration under FIFRA). A pesticide registration is a recognized property right under FIFRA. *See Indus. Safety Equip. Ass'n v. EPA,* 656 F. Supp. 852, 856 (D.D.C. 1987), *aff'd*, 837 F.2d 1115 (D.C. Cir. 1988) ("It is well settled that an agency license can create a protectible [sic] property interest, such that it cannot be revoked without due process of law."); *Reckitt Benckiser, Inc. v. Jackson,* 762 F. Supp. 2d 34, 45 (D.D.C. 2011) ("A FIFRA registration is essentially a license to sell and distribute pesticide products in accordance with the terms of the registration and the statute."); Mem. & Order, *Pesticide Action Network of N. Am. v. EPA,* No. C 08-1814 MHP, at 4 (N.D. Cal. July 8, 2008), ECF No. 43 ("The registrations involved here are essentially government licenses to produce, distribute and sell pesticides . . . [and] therefore constitute property[.]"). FIFRA governs cancellation of pesticide registrations and affords the registrant certain process before a registration may be cancelled. This includes the requirement that EPA convene an SAP to provide comments to the Agency on "the impact on health and the environment" of proposed cancellation actions. FIFRA § 25(d)(1), 7 U.S.C. § 136w(d). Should EPA proceed with tolerance revocation and bypass further peer review, EPA would essentially be making an end-run around FIFRA's requirements, in violation of DAS's Due Process rights.

EPA's own guidance indicates that peer review is appropriate in these circumstances. EPA's Peer Review Handbook states that "external peer review is the *expected procedure*" for "highly influential scientific assessments." EPA Peer Review Handbook, App'x A at A-4 (4th ed. 2015) (emphasis added). Independent peer review is also warranted by EPA's Science Advisory Board. 42 U.S.C. § 4365. Given the enormous ramifications and potentially precedent-setting impact of EPA's proposed revocation of all tolerances for chlorpyrifos—one of the most

widely used pest management products in the world—EPA must convene an SAP to conduct external peer review of its 2016 RHHRA before issuing a final rule.

VII. EPA's Reliance on the Columbia Study Without the Raw Data is Arbitrary and Capricious, Violates Due Process, and Contravenes EPA's Statutory Obligations and Executive Branch Directives.

EPA's reliance on the Columbia study to revoke all tolerances for chlorpyrifos without obtaining and reviewing the underlying raw data is arbitrary and capricious, in violation of the Administrative Procedure Act ("APA"). *See* 5 U.S.C. § 706(2)(A) (instructing courts to hold unlawful and set aside agency action held to be arbitrary and capricious, an abuse of discretion, or not in accordance with the law); *see also Motor Vehicle Mfrs. Ass'n v. Ruckelshaus*, 719 F.2d 1159, 1164 (D.C. Cir. 1983) (agency action arbitrary and capricious if it *fails to examine relevant data*). Without all of the raw data from the Columbia Study, EPA cannot meet its statutory obligations under the FFDCA to properly consider "the validity, completeness, and reliability of the available data from studies of the pesticide." FFDCA § 408(b)(2)(D)(i), 21 U.S.C. § 346a(b)(2)(D)(i). For example, without the underlying data from the Columbia study, results cannot be replicated and are therefore not reliable under the FFDCA. *See also, e.g.,* Dow AgroSciences LLC's Response to EPA Revised Human Health Risk Assessment for Chlorpyrifos Registration Review, EPA-HQ-OPP-2008-0850-0845 at 34–37 (Apr. 29, 2015); Dow AgroSciences LLC's Additional Comments to EPA's Chlorpyrifos Issue Paper, 2016-0062-0123 at 6–7 (Apr. 16, 2016).

A revocation of tolerances without reliable data also raises serious Due Process concerns. DAS is concerned that EPA's use of the Columbia study, for which the Agency lacks supporting data and that is refuted by an abundance of quantitative science, sets a double standard for academic researchers and members of the regulated community. EPA commonly requests raw data from pesticide registrants on studies they submit, and DAS and other registrants routinely provide and maintain such data for Agency review to ensure a thorough, high-quality risk assessment. Not holding federally funded researchers to the same standard creates a glaring inconsistency in light of EPA's stated principles of scientific integrity in regulatory matters and raises serious Due Process concerns with respect to the Agency's revised risk assessment for chlorpyrifos in the absence of the underlying epidemiology data. *See Indus. Safety Equip. Ass'n*, 656 F. Supp. at 865 (agency license can create a protectable property interest that "cannot be

revoked without due process of law"); *Reckitt Benckiser, Inc*., 762 F. Supp. 2d at 45 ("A FIFRA registration is essentially a license to sell and distribute pesticide products").

Several courts have held that an agency must have and make available all of the raw data underlying a study in order to rely on that study for rulemaking, and that such data must be "reliable." *See, e.g., United States v. Nova Scotia Food Prods. Corp.*, 568 F.2d 240, 251 (2d Cir. 1977) (failure to disclose scientific data relied upon by agency in fashioning a proposed rule prevented the agency from considering all "the relevant factors," made the rule procedurally erroneous and therefore invalid); *NRDC v. EPA*, 658 F.3d 200, 218 (2d Cir. 2011) (EPA had acted in an arbitrary and capricious manner by relying on a study that was not "reliable data" to lower the FQPA safety factor); *Endangered Species Comm. of Bldg. Indus. Ass'n v. Babbitt*, 852 F. Supp. 32, 36–38 (D.D.C. 1994), *as amended on reconsideration* (June 16, 1994) (observing that "where an agency relies upon data to come to a rulemaking decision, it generally has an obligation under the APA to provide such data for public inspection[,]" and holding that agency's failure to make data available to interested parties violated the APA). *See also Zero Zone, Inc. v. U.S. Dep't of Energy,* 832 F.3d 654, 670 (7th Cir. 2016) (observing that "[s]everal of our sister circuits have held that among the information that must be revealed for public evaluation are the technical studies and data upon which the agency relied") (internal quotation marks and citation omitted).

In connection with the 2016 SAP, EPA relied on *Coalition of Battery Recyclers Ass'n v. EPA*, 604 F.3d 613 (D.C. Cir. 2010), and *American Trucking Ass'ns v. EPA*, 283 F.3d 355 (D.C. Cir. 2002) for the proposition that it need not obtain the raw data. Both cases are readily distinguishable. In *Coalition for Battery Recyclers*, the petitioners failed to raise the need for the raw data until rebuttal at oral argument, and failed to identify errors that would make reliance on the study at issue arbitrary and capricious. In *American Trucking*, the agency was not relying on a taxpayer funded study to take unprecedented regulatory action in the absence of underlying raw data, nor was there any indication that EPA failed to request and disclose the data in response to a FOIA request pursuant to OMB Circular A-110. In contrast, here, EPA is required to request and disclose the raw data underlying the Columbia study, which was supported by federal funds, in response to numerous FOIA requests submitted by DAS and others (most recently on August 19, 2016), pursuant to OMB Circular A-110, and EPA itself has repeatedly requested the raw data from the Columbia researchers, who have refused to provide them. *See* Appendix C. In

addition, *American Trucking* was decided before the Obama Administration's push for greater data transparency in scientific decision-making.

In addition to being unsupported by case law, EPA's reliance on the Columbia study—to the exclusion of a complete database of toxicological studies and in the absence of supporting raw data—contravenes the Agency's policies of data access and transparency in scientific decision-making. *See* President Obama's Mem. on Scientific Integrity (Mar. 9, 2009) ("[T]here should be transparency in the preparation, identification, and use of scientific . . . information in policymaking."); EPA Administrator Jackson Mem. to EPA Employees (May 9, 2009) ("Our regulatory decisions should include a full explanation of the science issues addressed," including "the data relevant to those issues."). EPA's reliance on the Columbia study without obtaining the underlying raw data also violates OMB Circular A-110, which mandates the public disclosure of data underlying federally funded studies used to develop agency action that has the force and effect of law. Indeed, EPA itself has recognized the importance of the raw data, having requested it from the Columbia researchers on numerous prior occasions. Jan. 25, 2013 Ltr. from S. Bradbury to PANNA and NRDC, (Jan. 25, 2013), *PANNA v. EPA*, No. 14-72794, Ex. 8 at 4 (9th Cir. Sept. 10, 2014) ECF No. 1-2 (Columbia study authors had "declined [EPA's] request to provide" the raw data). Despite the fact that the Study was supported with taxpayer funds, the study's authors have steadfastly refused EPA's requests.

VIII. EPA's Use of a 10X FQPA Safety Factor is Unfounded.

DAS has made it abundantly clear in its prior comments that EPA's increase of the FQPA safety factor from 1X in the Agency's 2011 PHHRA to 10X due to "uncertainty" derived by the Agency on the basis of the Columbia study and other epidemiology studies as well as EPA's shift in policy on chlorpyrifos is not consistent with the FFDCA. *See* Appendix A. Safety factors, including those used to propose tolerance revocation, must be based on valid and reliable data. FFDCA § 408(b)(2)(D), 21 U.S.C. § 346a(b)(2)(D). Uncertainty caused by EPA's failure to obtain the underlying raw data for the Columbia study and other epidemiology studies[10] in order to assess the validity and reliability of these studies is not a basis to apply a 10X safety factor and revoke tolerances. Nor is a shift in Agency regulatory policy justified on this basis.

[10] Epidemiology studies that did not specifically deal with chlorpyrifos are not "studies of the pesticide chemical and pesticide chemical residue[s]" and thus are not relevant in any event to the 2016 RHHRA for chlorpyrifos. FFDCA § 408(b)(2)(D), 21 U.S.C. § 346a(b)(2)(D).

This is especially true when: (a) there is no new data or science since the 2011 PHHRA to warrant this reversal; (b) a scientific weight of evidence review that includes both animal and human data supports the conclusion that chlorpyrifos exposure below the current regulatory standard is not associated with neurodevelopmental effects; and, (c) the current PoD based on RBC ChEI for chlorpyrifos is protective of human health.

Moreover, the 2016 SAP's conclusions regarding the cord blood information reported in the Columbia study actually *support* the PHHRA's determination of a 1X safety factor for chlorpyrifos. By finding that the cord blood test results reported in the Columbia study are not reliable, the SAP essentially negated the conclusions that the Columbia researchers reached on the basis of those test results. Thus, the SAP not only removed any "uncertainty" that could be founded on the Columbia study for risk assessment purposes, but also demonstrated why it is so important for the raw data for studies of this nature to be accessible and carefully reviewed before any regulatory action is proposed, let alone action of such an unprecedented nature.

In its 2016 RHHRA, EPA discloses, for the first time, a new basis for the application of a 10X safety factor. EPA contends that the chlorpyrifos blood level it estimated from the crack and crevice application methodology is likely to be a LOAEL (lowest observed adverse effect level) rather than a NOAEL (no observed adverse effect level), and that it is EPA's policy to apply a 10X safety factor in such situations. However, this approach is simply inapplicable to this situation. The LOAEL/NOAEL applies when there is a defined dose-response relationship. Yet there is no defined dose-response relationship in the 2016 RHHRA's approach to chlorpyrifos, especially now that the Agency has discarded the "high" and "low" exposure group distinction in the Columbia study and applied a single TWA. *See supra*, Section VI.C. EPA's 2016 RHHRA is essentially one where unrealistically "measured" exposures through the inherently faulty approach based on assumptions about crack and crevice applications have generated unmeasured, undefined effects. This is no place for application of a 10X safety factor based on LOAEL/NOAEL (and this is certainly not a basis to change the current regulatory standard for chlorpyrifos).

Moreover, discussion of LOAEL/NOAEL is traditionally reserved for experimental toxicology studies that specifically and purposely involve at least three dose levels, thus allowing for the identification of a no-effect level, a lowest-observed effect level, and a maximum

tolerated dose level. Epidemiology studies by their very nature are not designed to establish and then "test" various dose or exposure levels in humans, and hence, there is no basis for EPA inferring that a particular exposure and concomitant blood level represent a particular "effect level"—in this case a LOAEL from the Columbia study. Furthermore, DAS is not aware of previous EPA actions whereby epidemiological studies were evaluated relative to the determination of LOAEL/NOAELs and therefore this current iteration of a 10X safety factor based on the Columbia study is unprecedented, unreviewed by EPA's SAP or Science Advisory Board, and without any scientific basis or rationale.

References:

EPA, Transmittal of Meeting Minutes of the April 19-21, 2016 FIFRA SAP Meeting Held to Consider and Review Scientific Issues Associated with "Chlorpyrifos:Analysis of Biomonitoring Data," (July 20, 2016).

Food Quality Protection Act (FQPA) Expert Panel. October 17, 2016.

SciPinion, 2016. Peer Review of Physiologically Based Pharmacokinetic/Pharmacodynamic Model for Chlorpyrifos. November 1, 2016.

EPA, Chlorpyrifos: Preliminary Human Health Risk Assessment for Registration Review (June 30, 2011).

EPA, Chlorpyrifos: Revised Human Health Risk Assessment for Registration Review (Dec. 29, 2014).

EPA, Chlorpyrifos: Revised Human Health Risk Assessment for Registration Review (Nov. 3, 2016).

IX. EPA Lacks a Scientific Justification for Setting a 10X Intraspecies Uncertainty Factor.

EPA has retained a 10X Intraspecies Uncertainty Factor based on its initial conclusion that the PBPK model for chlorpyrifos does not adequately address the life-stage of pregnancy. However, DAS has updated the model recently to account for this life-stage, and DAS had this this work peer-reviewed by independent external experts. *See* SciPinion LLC, 2016, attached as Ex. 6. This group concluded that the recent expansion of the model to accommodate important life-stage changes that occur during pregnancy are sufficiently robust and validated to allow its use by the EPA and other regulatory bodies globally for risk assessments involving pregnant

women. As such, EPA should be able to now reduce the intraspecies uncertainty factor for pregnant or women of childbearing age to 4X.

In the 2014 RHHRA, EPA utilized the PBPK model for chlorpyrifos to reduce the intraspecies extrapolation factor from 10x to 4x for the general population, but no reduction was made for the women of childbearing age, as the PBPK model did not incorporate pregnancy at that time.

To investigate the appropriateness of this 4x extrapolation factor for pregnant women, the current PBPK model was expanded to include systemic exposure and cholinesterase effects predictions during all stages of human pregnancy in April 2015 (*Poet* 2015). Monte Carlo analyses were then conducted with this updated PBPK model and the results showed that the 4x extrapolation factor is applicable to pregnant women as well.

In the 2016 Chlorpyrifos Issue Paper (EPA 2016), EPA acknowledges these upgrades to the PBPK model. However, the Agency expresses reservations on the validity of the model, as follows:

> While the modified model reasonably simulated the physiological changes during pregnancy, the model's predictive ability to simulate internal dosimetry of chlorpyrifos cannot be properly evaluated since there are no chlorpyrifos-specific pharmacokinetic data available during pregnancy. **As such, the agency cannot evaluate its predictive capacity and thus, the pregnancy model will not be used for risk assessment at this time.**

Chlorpyrifos Issue Paper at 16 (emphasis in original).

To the contrary, all major physiological parameters in the pregnancy model were based on well-characterized datasets:

- Addition of placenta and fetal compartments, which grow over the course of pregnancy
- Pregnancy specific changes in the slow compartment, fat, and rapid compartments
- Pregnancy specific changes in blood composition
    - Changes in blood composition result in increased blood volume, decreased hematocrit
    - Lipids, triglycerides, and cholesterol increase – leads to changes in partitioning

In addition, the critical chlorpyrifos-specific pharmacokinetic/metabolism parameters in this model were also based on well-measured values:

- The changes in blood:tissue partitioning were based on changes in plasma lipid levels, as well as relative differences in partitioning across gestation, in tissues from both pregnant rat and human donors, as described in *Lowe* et al. (2009).

- Pregnancy-related changes in metabolism were also based on measured values:

    - CYP isoform contributions to overall chlorpyrifos activation to the oxon metabolite or detoxification to TCPy were based on experimental *in vitro* data from human CYP enzymes (*Foxenberg* et al. 2007).

    - Pregnancy-based changes in specific CYP levels were obtained from a variety of literature sources (*Dickmann* and Isoherranen 2013, *Mohamed* 2013, *Pennell* 2003, *Sit* 2008, *Tracy* 2005). These values were utilized to calculate gestational time-dependent metabolic rate constants for CYP metabolism, as per methods described in *Foxenberg* et al. 2011 and overall trends reported by *Abduljalil et al.* 2012.

    - Pregnancy related changes in PON1 activity for oxon metabolite hydrolysis were included in the revised PBPK model, and based on several measured datasets (*Huen* et al. 2010, *Sarandol* et al. 2010, *Smith* et al. 2014).

These important changes are included in the CPF model for pregnancy, built on the life-stage platform so either age-specific parameters or initial body weight-specific parameters can be used as the initial condition at the beginning of gestation. All model additions, changes, mathematical implementations, and model code are included in the Pregnancy PBPK model report, submitted to the US EPA in April 2015 (*Poet* 2015). The predictive function of a PBPK model is based upon the use of realistic anatomical, physiological and biochemical compartments. The CPF model has validated all of these major changes in pregnant women over time. Based on these clarifications, DAS feels that the revised version of the PBPK model is functional for predicting both chlorpyrifos pharmacokinetics and pharmacodynamics over the course of human pregnancy. **Therefore, EPA should utilize the model-derived intraspecies extrapolation factor of 4x for all human life-stages.**

DAS engaged SciPinion (SciPinion, 2016) to recruit a panel of experts to review the PBPK model for its appropriateness in evaluation of the life-stage during pregnancy. Results of the peer review revealed the following:

- The entire panel agreed that (a) the physiological and biochemical underpinnings of the model permit their use to effects for which data may not be available (e.g., chlorpyrifos blood concentrations and cholinesterase inhibition in pregnant women) and (b) that key changes in physiology during pregnancy are accurately reflected and appropriately incorporated into the latest revisions of the life-stage PBPK/PD model.

- In the opinion of a majority (a) important chlorpyrifos-specific parameters (e.g., interindividual enzyme activity) and (b) inter-individual variation in sensitivity and the use of advance modeling techniques to evaluate pregnant women have been incorporated into the model.

- Importantly, a majority of the panel agreed that model predictions of chlorpyrifos exposure and effects in pregnant women are as well-developed and validated as other PBPK models that have been used for regulatory risk assessment.

Peer Review of Physiological Based Pharmacokinetic/Pharmacodynamic (PBPK) Model for Chlorpyrifos (Nov. 1, 2016).

Results of this independent peer review of the PBPK/PD model for chlorpyrifos indicate that the recent expansion of the model to accommodate important life-stage changes that occur during pregnancy are sufficiently robust and validated to allow its use by the EPA and other regulatory bodies globally for risk assessments involving pregnant women.

References:

Abduljalil, K., Furness, P., Johnson, T.N., Rostami-Hodjegan, A., Soltani, H., 2012. Anatomical, physiological and metabolic changes with gestational age during normal pregnancy: a database for parameters required in physiologically based pharmacokinetic modelling. Clin. Pharmacokinet. 51, 365–96. doi:10.2165/11597440-000000000-00000

Dickmann, L.J., Isoherranen, N., 2013. Quantitative prediction of CYP2B6 induction by estradiol during pregnancy: potential explanation for increased methadone clearance during pregnancy. Drug Metab. Dispos. 41, 270–4. doi:10.1124/dmd.112.047118

EPA, Chlorpyrifos: Revised Human Health Risk Assessment for Registration Review (Nov. 3, 2016)

EPA, Chlorpyrifos: Revised Human Health Risk Assessment for Registration Review Dec. 29, 2014).

Foxenberg, R.J., McGarrigle, B.P., Knaak, J.B., Kostyniak, P.J., Olson, J.R., 2007. Human hepatic cytochrome p450-specific metabolism of parathion and chlorpyrifos. Drug Metab. Dispos. 35, 189–93. doi:10.1124/dmd.106.012427

Huen, K., Harley, K., Bradman, A., Eskenazi, B., Holland, N., 2010. Longitudinal changes in

PON1 enzymatic activities in Mexican-American mothers and children with different genotypes and haplotypes. Toxicol. Appl. Pharmacol. 244, 181–9. doi:10.1016/j.taap.2009.12.031

Lowe, E.R., Poet, T.S., Rick, D.L., Marty, M.S., Mattsson, J.L., Timchalk, C., Bartels, M.J., 2009. The effect of plasma lipids on the pharmacokinetics of chlorpyrifos and the impact on interpretation of blood biomonitoring data. Toxicol. Sci. 108, 258–72. doi:10.1093/toxsci/kfp034

Mohamed, A.M.N.A., 2013. Nifedipine pharmacokinetics and pregnancy: Studies on clearance, absorption, and transport. Theses Diss. Available from ProQuest.

Pennell, P.B., 2003. Antiepileptic drug pharmacokinetics during pregnancy and lactation. Neurology 61, S35-42.

Poet, T. S. 2015. Multi-Route, Lifestage and Pregnancy PBPK/PD Model for Chlorpyrifos and Chlorpyrifos-oxon: Model development and validation. Submitted to Docket 4/2015. Study ID: NS000197

Sarandöl, E., Dirican, M., Eröz, E., Serdar, Z., Uncu, G., 2010. SERUM PARAOXONASE AND ARYLESTERASE ACTIVITIES THROUGHOUT NORMAL PREGNANCY. Nobel Med. 19, 49–55.

SciPinion LLC. 2016. Peer Review of Physiologically Based Pharmacokinetic/Pharmacodynamic Model for Chlorpyrifos. Submitted to docket:EPA-HQ-OPP-2015-0653 January, 2017.

Sit, D.K., Perel, J.M., Helsel, J.C., Wisner, K.L., 2008. Changes in antidepressant metabolism and dosing across pregnancy and early postpartum. J. Clin. Psychiatry 69, 652–8.

Smith, J.N., Hinderliter, P.M., Timchalk, C., Bartels, M.J., Poet, T.S., 2014. A human life-stage physiologically based pharmacokinetic and pharmacodynamic model for chlorpyrifos: Development and validation. Regul. Toxicol. Pharmacol. 69, 580–597.

Tracy, T.S., Venkataramanan, R., Glover, D.D., Caritis, S.N., 2005. Temporal changes in drug metabolism (CYP1A2, CYP2D6 and CYP3A Activity) during pregnancy. Am. J. Obstet. Gynecol. 192, 633–9. doi:10.1016/j.ajog.2004.08.030

X. EPA's Use of An Inappropriate PoD Results in Unrealistic Estimates of Risk that Have No Basis in Fact.

EPA's generation of a TWA blood level based on flawed assumptions about alleged crack and crevice chlorpyrifos use nearly two decades ago and an epidemiology study the SAP has deemed unreliable has culminated in an unfounded estimate of risk for all populations and exposure scenarios.

Dietary exposure calculations have remained very steady over the years; DAS agrees with the Agency's highly refined dietary exposure assessments. It is the change in the PoD that has resulted in an implausible estimated dietary risk. Additionally, the inappropriate application of an FQPA safety factor to occupational risk assessment leads to an overestimate of risk and

departs from the FFDCA's statutory text and intent. EPA's new residential post-application and bystander risk assessments also lack plausibility/reasonableness. DAS concurs with the residential post-application exposure assessment presented in the 2014 RHHRA, which concluded that there were no risks of concern. EPA used these same exposures in the 2016 RHHRA, but this time in tandem with the inappropriate PoDs and LOCs. As a consequence, the 2016 assessment overestimated risk and improperly concluded that all residential risks assessed with the updated PBPK-derived PoDs are of concern. Similarly, the 2016 RHHRA grossly overestimated bystander risk. In doing so, EPA ignored studies described by the Agency in 2014 as "high-quality nose-only vapor phase [AChE inhibition] inhalation toxicity studies" 2014 RHHRA at 83-84. These studies demonstrated that no toxicity (*i.e.*, no hazard) occurred at even the maximum achievable inhalation dose (saturation concentration), and based on these studies, the Agency concluded in the 2014 RHHA that there was no risk potential to bystanders. DAS concurs with the 2014 RHHRA that there are no anticipated risks of concern from exposure due to the volatilization of either chlorpyrifos or chlorpyrifos oxon, but vigorously disagrees with EPA's use of the inappropriate PoD methodology in its 2016 RHHRA.

A. EPA's Dietary Risk Estimates Lack Plausibility/Reasonableness.

Dietary exposure calculations have remained very steady over the years; DAS agrees with the Agency's highly refined dietary exposure assessments. It is the change in the PoD based on the Agency's inappropriate reliance on the Columbia study and flawed exposure assessment that has resulted in a highly unrealistic estimated dietary risk. Table X.1 illustrates the steady exposure from food over the course of EPA's recent review of chlorpyrifos for two example sub-populations. The Table illustrates the dramatic shift in EPA's assessment and highlights how the application of EPA's new methodology to derive a new point of departure unrealistically estimates risk.

The Table also shows that the new PoD (based on post-application crack and crevice exposure) was selected because it is much lower than the food exposure and thus yields an even lower acceptable dose.

Table X.1. Chronic and Steady State Dietary (Food Only) Exposure and Risk Estimates for Chlorpyrifos

Year/document	PoD (µg/kg/day)	PAD (µg/kg/day)	Food exposure (µg/kg/day)	Exposure as % of PAD
Children 1-2 yrs				
2011 Preliminary HHA	30 ($BMDL_{10}$)[a]	0.3 (cPAD)	0.025	8.4
2014 Revised HHA	99 (ssPoD) [a]	2.5 (ssPAD)	0.242	9.7
2015 Proposed Rule	99 (ssPoD) [a]	2.5 (ssPAD)	0.242	9.7
2016 Revised HHA	0.17 (ssPoD)[b]	0.0017 (ssPAD)	0.242	14,000
Adults (Females 13-49 yrs)				
2011 Preliminary HHA	30 ($BMDL_{10}$)[a]	0.3 (cPAD)	0.007	2.2
2014 Revised HHA	78 (ssPoD)[a]	0.78 (ssPAD)	0.075	9.6
2015 Proposed Rule	78 (ssPoD)[a]	0.78 (ssPAD)	0.075	9.6
2016 Revised HHA	0.12 (ssPoD)[b]	0.0012 (ssPAD)	0.075	6,200

$BMDL_{10}$= benchmark dose lower confidence limit for 10% RBC ChE inhibition
[a] PoD based on 10% RBC ChE inhibition
[b] PoD predicted by PBPK modeling of dietary exposure that would produce TWA of chlorpyrifos in blood of 0.004 µg/L (concentration predicted from crack and crevice exposure and implied to be associated with neurological effects)

B. EPA Has Inappropriately Applied an FQPA Safety Factor to Occupational Risk Assessment.

Occupational exposure does not fall under the ambit of the FFDCA, and therefore the 10X FQPA safety factor applied (inappropriately) to dietary exposures should not be applied to occupational exposure assessment. The EPA's proposed approach to chlorpyrifos continues a troubling trend by the Agency to depart from the carefully crafted provisions of FFDCA Section 408, as amended by the FQPA. As a case in point, Congress established the standard that EPA must use when establishing or leaving a tolerance in effect for a pesticide chemical residue. That standard requires that "the tolerance [must be] safe." FFDCA § 408(b)(2)(A)(i), 21 U.S.C. § 346a(b)(2)(A)(i).

> The term "safe" means that EPA has determined 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.

FFDCA § 408(b)(2)(A)(ii), 21 U.S.C. § 346a(b)(2)(A)(ii) (emphasis added). And Congress went on to define the term "pesticide chemical residue" to mean:

a residue in or on raw agricultural commodity or processed food of—

(A) a pesticide chemical; or

(B) any other added substance that is present on or in the commodity or food primarily as a result of the metabolism or other degradation of a pesticide chemical.

FFDCA § 201(q)(2), 21 U.S.C. § 321(q)(2) (emphasis added).

Based on the literal language of the FFDCA Section 408, aggregate exposure under the general safety standard applies to the "pesticide chemical residue"—*i.e.*, a residue "in or on food." EPA's attempt to shoehorn occupational exposure (and drinking water) into this standard raises serious legal and policy issues.

Further support for limiting the safety standard to pesticide chemical residues in or on food can be found in the companion amendments made to FIFRA by FQPA. Specifically, the definition of the pesticide registration standard was amended so that "a *human dietary risk* from residues that result from a use of a pesticide *in or on any food* inconsistent with the [safety] standard under section [408]" triggers a cancellation action for the relevant food uses of that pesticide. FIFRA § 2(bb), 7 U.S.C. § 136(bb) (emphasis added).

Based on the foregoing, the total uncertainty factor (UF) for occupational exposure in the 2016 RHHRA should be 10X and not 100X. Consequently, the Level of Concern (LOC) should be 10 and not 100.

Additionally, as was noted above for dietary exposure, chlorpyrifos exposure from the majority of occupational scenarios has remained steady over time because exposure is calculated using inputs from long-established exposure databases and methodology. Once again it is the new PoD that has resulted in the enormous differences in estimated risks for operators presented in the 2016 RHHRA's Appendix F compared to previous risk assessments. The impact of the new PoD combined with the inappropriate addition of the FQPA safety factor results in dramatically different occupational MOEs compared to those from previous risk assessments.

C. EPA's Residential Post-Application Risk Assessment Lacks Plausibility/Reasonableness.

DAS concurs with the residential post-application exposure assessment presented in the 2014 RHHRA, which concluded that there were no risks of concern. EPA used these same estimated exposures in the 2016 RHHRA, but this time in tandem with the updated and improperly derived PoDs and LOCs. Not surprisingly, as a result the 2016 RHHRA inappropriately concludes that all residential risks assessed with the updated PBPK-derived PoDs

based on alleged crack and crevice uses of chlorpyrifos during the time of the Columbia cohort are of concern.

D. EPA's Bystander Risk Assessment Lacks Plausibility/Reasonableness.

As set forth repeatedly herein, the PBPK-derived PoD based on alleged crack and crevice uses of chlorpyrifos during the time of the Columbia cohort is unrepresentative, unreliable and inappropriate for risk assessment. Use of the new improperly derived PoD leads to a dramatic departure from EPA's previous conclusions which were based on a wealth of robust, science-based data including a new study conducted specifically to address the risk from inhalation of chlorpyrifos.

The 2014 RHHRA comprehensively assessed the risk to bystanders via spray drift and volatilization and DAS concurs with the conclusions the Agency reached at that time that: (i) there are no anticipated risks of concern from exposure due to the volatilization of either chlorpyrifos or chlorpyrifos oxon; and, (ii) buffers of zero to twenty-five feet are protective of both adults and children 1 to <2 years old who may be exposed as a result of drift from treated fields.

The history of recent risk assessment for exposure to bystanders from spray drift is summarized by EPA in the 2016 RHHRA:

> 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 bystanders, chlorpyrifos technical registrants voluntarily agreed to lower application rates and to other spray drift mitigation measures.

2016 RHHRA at 30.

Spray drift mitigation measures and use restrictions have been in place on all chlorpyrifos agricultural labels since December 2012. In the 2014 RHHRA the Agency evaluated adult and children 1 to <2 years old spray drift buffer zones for aerial, groundboom and airblast applications and using several nozzle droplet types. Utilizing the PBPK-PD model, the Agency completed an updated assessment based on the PoD of 10% RBC AChE. DAS supports the Agency and the science-based decision using PBPK and the appropriate PoD, and agrees with the Agency conclusion indicating that buffers of zero to twenty-five feet are protective of both adults and children 1 to <2 years old who may be exposed as a result of drift from treated fields.

As such, buffer restrictions on product labels should be revised to reflect the conclusions of the 2014 risk assessment.

With regard to the risk from post-application inhalation exposure (from volatilization) the Agency conducted a preliminary assessment in 2013 that "indicated that offsite concentrations of chlorpyrifos and chlorpyrifos-oxon may exceed the target concentration based on the toxicological endpoints used at the time." 2016 RHHRA at 31. In response to this assessment, DAS conducted two inhalation studies for both chlorpyrifos and chlorpyrifos-oxon which were reviewed by EPA in the 2014 RHHRA as part of a re-evaluation of the 2013 preliminary assessment. The Agency described the studies as "high quality nose-only vapor phase inhalation toxicity studies." 2014 RHHRA at 83–84. These studies demonstrated that no toxicity (*i.e.*, no hazard) occurred at even the maximum achievable inhalation dose (saturation concentration), and the Agency concluded that there was no risk potential, as risk is a function of both exposure and hazard. *Id.* at 84.

DAS concurs with the 2014 RHHRA that there are no anticipated risks of concern from exposure due to the volatilization of either chlorpyrifos or chlorpyrifos oxon, but DAS is very concerned that EPA essentially ignored these studies for purposes of the 2016 RHHRA.

XI. EPA Is Relying on a Flawed Drinking Water Modeling Analysis.

A. Introduction

To calculate the potential for human exposure to pesticides through drinking water, EPA relies upon computer simulations. The Agency bills the updated drinking water assessment for chlorpyrifos (Bohaty and Hetrick, 2016; docket reference EPA-HQ-OPP-2015-0653-0437) as a highly-refined and final assessment and appropriate for use in a refined aggregate human health risk assessment. However, the assessment is inadequate for this purpose, as it is merely a slightly modified screening-level assessment. The input parameterization of the modeling consists of a series of compounding conservative factors and does not employ readily-available data and well-understood methodologies for defensible and straight-forward refinements that would much more realistically reflect the potential for human exposure.

The Agency clearly states, and DAS concurs, that the intensity of the use of a product will be a major determining factor in the magnitude of the potential residues in surface water bodies. However, EPA did not factor this concept into its assessment for chlorpyrifos. Instead,

EPA speculated that since a drinking water catchment *could contain* a high intensity of agriculture, then the Agency's assumption of treatment of an entire watershed, at the maximum labeled use rate, on the same day, was justified. The Agency further justified its assumptions by citing wide-area (non-crop) uses of chlorpyrifos; but most of these uses are no longer supported by DAS and even if occurred to parts of the watershed would likely not have occurred with the same timing and use pattern as any crop applications. The Agency claimed that its modeling was validated by comparison to monitoring data, when scaled to account for sampling bias. This comparison is at best of limited scientific validity.

As it stands, EPA's purported refined and final assessment is neither, as a lack of refined modeling, spatial reference and detail limits its utility for risk assessment. The Agency has ignored DAS's submissions and offers to collaborate on methodologies to refine the assessment, and has thus missed the opportunity to leverage these data and other information to advance the understanding of the potential impact of chlorpyrifos upon surface water resources.

EPA is basing the assessment of risk through drinking water using approaches which are outdated and fail to implement the most current and available methodology. Refinement methodologies have been provided to EPA but are not included in the current assessment. EPA should bring these proposed refinement techniques to a SAP and seek guidance on how to make the Agency's assessments reflect the latest, best science before using an approach that was last reviewed eighteen years ago. In addition, EPA continues to rely on worst-case scenarios for key refinement parameters. The impact of such worst-case assumptions and guidance on how to determine and utilize more realistic assumptions should be addressed by a SAP. It is for these reasons that thirty-five U.S. agricultural organizations submitted a letter to Gina McCarthy, Administrator, U.S. EPA (dated January 12, 2017), requesting that EPA convene a SAP to consider EPA's approach and methodology used in the drinking water assessment for chlorpyrifos. *See* Ex. 1.

B. EPA's Current Drinking Water Assessment Is Not Highly Refined and Is Incomplete.

EPA describes its current drinking water assessment as "highly refined." This is an incorrect characterization, as the work is little more than a slightly modified screening-level assessment. This is primarily due to the overriding assumption that the entire area of any drinking water catchment where chlorpyrifos is labeled for use will receive applications on the

same day, at the maximum use rate, with additional applications occurring at the shortest labeled retreatment interval. This, in conjunction with an exposure model parameterized to reflect a highly-vulnerable watershed, along with other conservative assumptions, leads to extreme estimates of potential drinking water concentrations that are not reflective of the real-world use of the product.

The Agency clearly states, and DAS concurs, that the intensity of the use of a product will be a major determining factor in the magnitude of the potential residues in water bodies. A well-accepted way of reflecting the intensity of use is through the use of Percent Cropped Area ("PCA"), which are adjustment factors representing the fraction of a catchment covered by a given land cover or treated crop. Modeled Estimated Drinking Water Concentrations ("EDWC") for each crop in the catchment are then simply multiplied by the corresponding PCA and the results summed to give an adjusted EDWC.

In previous guidance (USEPA, 2014), EPA described methodology for defining PCA factors for a nationwide set of community water systems ("CWS") for some major crops. The drinking water intakes and corresponding watersheds in this guidance (the "CWS-DWI" dataset)[11] are based upon a 2012 extraction of data from EPA's Office of Water comprehensive Safe Drinking Water Information System ("SDWIS"). In the current drinking water assessment for chlorpyrifos, EPA discusses the CWS-DWI dataset in some detail and states that "there are a lot of data that can be utilized in deriving exposure estimates based on the CWS DWI PCA" Drinking Water Assessment at 63, but EPA recommends a PCA of 1 because of "the extent of chlorpyrifos uses including adult mosquito control, golf course turf, and general wide area use" Drinking Water Assessment at 88. However, such uses are not supported by DAS and thus the Agency's statement that "[i]f the chlorpyrifos use profile changes, the data are provided to easily facilitate investigation of the potential exposure without having to update this assessment," i*d.* at 64, is indeed applicable and further refinement by application of appropriate PCAs should be undertaken.

The Agency further insists on a PCA of 1 (*i.e.*, the entire watershed contains the crop under evaluation) because of a perceived lack of reliable data for some agricultural and vegetable

[11] It should be noted that registrants do not have access to these data, due to Department of Homeland Security restrictions.

crops. However, there are high-quality and readily accessible data available - the USDA Cropland Data Layer ("CDL"), for example. It should be noted that the 2014 CWS PCA Guidance indicates that the use of the CDL in place of the less detailed NLCD data "will be considered for future analysis" to update the CWS-DWI PCA values. The Agency has considerable experience with the CDL, and has defined it as "Best Available Data" in the Endangered Species Act context for defining potential product use areas (USEPA, 2016). In addition, MRID 50016001 (submitted by DAS to the Agency) offers a grouping technique to account for some of the uncertainties in vegetable classes which merits consideration.

The Agency additionally postulates that PCA refinement is not possible because of the possibility of small drinking water watersheds with high agricultural intensity, and recommends that the CWS-DWI dataset "be used to identify areas where exposure concentrations are expected to be higher" and further that "HUC-12 watersheds could be used as a surrogate … where watersheds were not delineated." Drinking Water Assessment at 63. However, the Agency goes on to say that with such an approach "the exposure could be underestimated," *Id*., since some of the specific CWS-DWI catchments and intakes may have changed over time; EPA also notes that some drinking water catchments might be smaller than HUC-12s and, thus, that the surrogates may be underpredictive. Changes in intakes or catchments no doubt happen, but they do not completely negate the usefulness of the CWS-DWI—there is no reason to believe that the overall distributions of surface water source drainage catchment sizes and populations, for example, would have changed drastically in a few years' time. These issues clearly point to the need for further analysis to identify specific areas with higher exposure potential for true drinking water watersheds, such as the concepts discussed in the September 2015 meeting with EFED (summarized in EPA-HQ-OPP-2008-0850-0853) (September 2015 EPA Meeting"), as well as the approach presented in DAS's Preliminary Refined Drinking Water Assessment (MRID 50016001), submitted in February 2016.

The data used in generating Figure 10 of the EPA assessment and the discussion preceding it highlight some of the refinement opportunities if the CWS-DWI database were to be more fully utilized. Drinking Water Assessment at 56-60. In addition to DA to NC ratios or field size to surface area ratios that can be evaluated (these are fixed in the Index Reservoir ("IR") modeling framework), the data would allow for testing of assumptions, for example, of vulnerable soils and drainage area to waterbody ratios for actual watersheds to determine when

the IR is a good surrogate or when refinements are required. The data would allow the Agency to make progress in identifying modeling frameworks that would better represent actual conditions. The assumptions of treatment on same day, relatively stagnant reservoir and simple direct drift to contributing water load can all be evaluated and refined with the data available to the Agency. Inclusion of flowing system hydrology, particularly when considering 21-day concentrations, is critical in identifying areas of concern.

The current EPA drinking water assessment claims to perform regional refinement of the exposure potential of chlorpyrifos. This was done, albeit superficially, by reflecting regional/state labeling restrictions in the modeling and using the CDL and USDA Census of Agriculture data to determine whether a certain crop is indeed grown within a given HUC-2. The assessment still relies upon the long-established set of standard soil/cropping/weather scenarios parameterized within the IR framework for use in the Pesticides in Water Calculator ("PWC") model, with some minor modifications. The IR conceptual model itself is an extreme case. As described in comments to the 2014 assessment (Reiss, 2015), although the Agency has appropriately characterized the IR drainage as a 90th percentile case based on a Drainage Area to Normal Capacity ratio (Jones et al. 1998), additional assumptions render the scenario non-representative of real-world conditions.

If a model input scenario for a crop of interest did not spatially exist in the HUC-2 of interest, "surrogate scenarios" for the simulated crop groups were selected from an adjacent HUC-2, parameterized with the highest runoff curve number, as representative of the highest runoff potential. This approach would not necessarily select the scenario with the highest runoff, as the runoff is also a function of the rainfall intensity and timing in relation to chemical application events. EPA's methodology is similar to the approach employed in the DAS submission of Feb 2016 (MRID 50016001); that submission also included the building of additional scenarios, if none were available in a given or adjacent HUC-02.

In selecting weather scenarios for the surrogates, the Agency selected the SAMSON weather station within the HUC-02 with the median 30-year total rainfall as representative. When a large range was seen in the total rainfall, some HUC-02s were divided into a low and high group (i.e., two weather scenarios were simulated). It is not known if this approach over- or under-estimates runoff for a given soil/crop scenario. Given the large spatial extent of the HUC-

02's and factors such as elevation and coastal effects, a more science-based approach would be to select weather scenarios on a more spatially-specific basis, such as was done in DAS's submission (MRID 50016001). Even this would still be, in actuality, a screening-level assessment. A much deeper understanding of the potential exposure risk could be explored with readily available spatial data. For example, more spatially-relevant scenarios could be developed by using CDL data on cropping, overlapped with the specific soils data (SSURGO, for example) along with detailed historical weather data. Such spatially-specific approaches have been presented by industry in the past. Indeed, similar concepts under development by the Agency in the new SAM model framework offer an opportunity to move beyond the scenario-based approach, and work to identify actual areas of greater or lesser vulnerability within the agricultural landscape.

EPA endeavored to explore the relative contributions of other modeling input parameters to the EDWCs via a limited sensitivity analysis. The Agency concluded from this effort that changes in environmental fate parameters, runoff curve numbers and application dates "are not expected to alter the risk assessment conclusions." The basis of this conclusion was not a statistical evaluation of sensitivity, but merely observations of the magnitude of modeled output changes resulting from using the bounds of input parameters. In addition, only one parameter was varied at a time, which neglects any interaction between the variables. From these observations, EPA concluded that changes of two- to three-fold were insignificant. However, depending upon the hazard endpoint used in the risk assessment, such changes may indeed be significant and should not be discounted out of hand.

EPA demonstrated a similar mindset through the continued use of absolute maximum application rates and minimum repeat intervals for the simulations, which can have a very significant impact upon the modeled results. In the context of a refined assessment, as EPA represented its effort to be, the use of more typical (and even regionally-dependent) application rates should have been explored. Such an analysis has been performed previously, for example in the work of Soloman et al. (2014).

C. EPA's Drinking Water Assessment Results Are Not Useful for Decision-Making and Do Not Reflect Real-World Observations.

The results of EPA's regional exposure modeling are presented as ranges of EDWC values by HUC-2 and the results of the individual crop simulations are available from the docket.

Since all of the simulations assume a PCA of 1 (the entire cropped area is planted in that crop and treated), within an indeterminate, extremely vulnerable catchment, it is unclear how the results would be used in a refined aggregate human health assessment to realistically reflect the overall use of the product. At this still-screening level, such results are only useful in the most basic exceedance context or to identify uses that may be of particular concern, since the results lack any spatial reference beyond the very large HUC-2 regions (the smallest in the Continental U.S. is about 41,000 square miles in area). If modeled results are to be used for quantitative purposes, modeling must be examined in a more spatially-explicit context, incorporating a more realistic representation of product use, and hopefully of the landscapes of actual drinking water catchments themselves. As was noted previously, such interpretations can also serve to direct further investigations of local conditions and the potential need for locally-specific management or to identify monitoring locations.

In its examination of the monitoring data available for chlorpyrifos, the Agency presents analyses of fifteen chlorpyrifos and five chlorpyrifos-oxon datasets collected within the United States. The fifteen chlorpyrifos datasets can be divided into two categories: those with full every-day sampling (one dataset) and those with incomplete daily sampling (fifteen datasets). All chlorpyrifos-oxon datasets have incomplete sampling.

The dataset with full every-day sampling was collected by the registrant at Orestimba Creek, CA and includes measurements at three sites on the creek. This dataset is also the only targeted monitoring dataset for chlorpyrifos identified in the assessment. Drinking Water Assessment at 90. Because daily sampling was used, both the 1-day and 21-day max can be calculated without interpolation of non-sampled days at each site-year. Since the three sites are on the same water system, the readings are positively correlated across the site-years, suggesting that the data are effectively one site, of little use for a national evaluation. Because of this, these data are ultimately of more use for model evaluation and method development. This was done in the Agency's analysis, which clearly showed the importance of reflecting the use intensity in a catchment, because when approximate PCAs were used in a more detailed modeling representation of the Orestimba, the Agency concluded "[t]herefore, it is expected that the model estimated chlorpyrifos concentrations provide a reasonable upper bound of concentrations that may occur in the environment based on the modeled use and PCA applied." Drinking Water Assessment at 118 (emphasis added).

For the other monitoring datasets, the calculation of time-weighted average concentrations for exposure assessment are complicated by the numerous non-detect samples (censored data) and by the many non-sampled days with no concentration readings.

Many statistical methods are available to adjust for the impact of data censoring on an analysis (Hensel, 2005). The extensive non-detections present with chlorpyrifos require considerable effort to defend a particular method or substitution value. Chlorpyrifos monitoring data are characterized by substantial censoring, causing the ½ LOD substitution used in the analyses of pages 98-113 of the Drinking Water Assessment to have a high degree of influence on the calculations. A more complete approach would be to generate the estimates as a bounding exercise, providing a lower bound analysis with zero substitution, and an upper bound with LOD substitution. This is especially important given the presence of sometimes large lab-specific LODs. As noted in the assessment, these large limits sometimes provide the largest yearly maxima and yet true values are most likely much less. If necessary, large lab-specific values can be subject to a separate sensitivity analysis; an example is shown in Mosquin et al. (2015).

The presence of non-sampled days introduces uncertainty in estimation and also estimation bias for some approaches and target quantities. Estimation uncertainty increases with the number of non-sampled days. Estimation bias can be large for the yearly maximum, which is estimated as the maximum in the sample, which in turn can be no larger than the true maximum over all days. Bias is less of a problem for the maximum 21-day rolling average, since as duration increases the bias decreases. The EPA Refined Drinking Water Assessment attempted to use bias factors to adjust for both uncertainty and bias.

Better methods exist for estimation than bias factors, including multiplicative factors and model-based approaches such as kriging and time series. These methods can also be modified to allow for protective values to be calculated. The bias factor depends on the sampling design, and for a given target quantity, its value increases as the sampling frequency decreases. For a given decision boundary (such as a DWLOC) the proportion of bias factor adjusted values exceeding that boundary will increase as the sampling frequency decreases. That is, the false positive rate goes up as the sampling frequency goes down. Furthermore, a bias-factor adjusted value, if presented on its own, does not give any information regarding the sampling frequency. For heavily censored data, such as those used for chlorpyrifos, bias factors should only be calculated

from site-years where the value of the bias factor is not affected by censoring assumptions, as there will be additional uncertainty added due to the censoring. For this reason, many of the site-years used in Table 69, Drinking Water Assessment at 115 to calculate bias factors are not suitable for that purpose.

The Agency also executed a modeled evaluation of chlorpyrifos with the WARP-MP model (Stone et al. 2013) and found the range of results to "reasonably compare" to the modeled output from the PWC model. However, this is not a fair comparison, because WARP-MP is modeling concentrations in streams while PWC is modeling a vulnerable static municipal reservoir.

EPA further states that the outputs from WARP-MP are representative because "estimated concentrations are derived based on monitoring data and as such reflect actual use data." Drinking Water Assessment at 114. This is incorrect. Data for chlorpyrifos were not included in the development and evaluation data sets of WARP-MP (see Table 1 in Stone et al.). The WARP-MP model uses the WARP model as its base, but with an adjustment factor (the Surface Water Mobility Index or "SWMI" (Chen et al. 2002)) based on chemical properties of a pesticide in question. Thus, WARP-MP was used to model chlorpyrifos concentrations by applying the adjustment factor for chlorpyrifos. There are additional issues with applying WARP-MP for quantitative exposure assessment and the WARP-MP developers recommend that the model is only appropriate for screening to identify high-risk watersheds and guiding targeted monitoring.

The Agency further claims that its modeling outputs are reliable because the results are within an order of magnitude of the surface water monitoring measurements, when corrected for sampling bias. DAS is not aware of the existence of a written statement in OPP FQPA science policy documents specifying that model accuracy within an order of magnitude is the degree of accuracy needed for human health risk assessment. EPA guidance requires this statement as a step in defining regulatory objectives (USEPA, 2009). This requirement was discussed in detail in previous comments (Oliver et al. 2015), but no definition of the regulatory objective has been supplied.

Because of all of these issues with the Agency's evaluation, its conclusions that the PWC modeled estimates are "reasonable" reflections of real-world conditions is further weakened and

again indicates that additional efforts are required to produce a scientifically defensible assessment.

D. EPA Has Not Responded to any Registrant Comments to Previous Assessments, Nor Has the Agency Considered or Referenced any Additional Submissions or Proposals from the Registrant.

EPA's efforts in the assessment of the potential for presence of chlorpyrifos in surface water resources spans a number of years, extending to the interim reregistration eligibility decision in 2001. In the current round of EPA Registration Review, the first drinking water assessment was released in 2011 (Bohaty, 2011). DAS, as the primary registrant, along with other members of the public, submitted detailed technical comments to the docket. In response to these comments, the Agency produced an updated drinking water assessment in 2014 (Bohaty, 2014). However, there were many technical areas that were not addressed in EPA's 2014 assessment. These deficiencies were again noted in comments that DAS submitted in April 2015, in response to the 2014 updated assessment (Oliver et al. 2015). There has been no response from EPA to these comments.

On September 10, 2015, EPA met with DAS to discuss possible refinement elements available for drinking water assessments (USEPA, 2015). DAS presented a proposal for data-driven refinement, which was not inconsistent with what EPA had presented in its December 2014 Revised Human Health Risk Assessment. In the summary of the meeting, EPA stated that "EPA will evaluate whether the proposal presented by DAS is appropriate to support refinements to risk assessments." September 2015 EPA Meeting at 1 (cover page). Such an evaluation was never received by DAS, nor was the meeting cited in the current assessment.

Since no feedback was received on the concepts proposed in the September 10, 2015 meeting, DAS undertook an effort to set forth these concepts in a refined national-scale assessment (Perkins et al. 2016; MRID 50016001), which DAS submitted to the Agency in February, 2016. EPA has not given any indication that they have undertaken any technical review of MRID 50016001, and EPA has made no formal or informal mention of the study, in the current assessment or elsewhere.

In the meantime, EPA was preparing the current drinking water assessment, whose transmission memorandum is dated April 14, 2016. However, the document was not released to the federal docket until late November, 2016. It is unfortunate that the Agency chose to withhold

the assessment for seven months when significant scientific progress could have been made to more realistically reflect the actual use of the product. The Agency has indicated that there are avenues for refinement of the assessment (for example, by the application of Percent Cropped Area (PCA) factors or reflecting label changes). However, it does not appear that EPA has any intention of engaging in refinement discussions, as the current assessment states: "This highly refined drinking water assessment updates and completes the Agency's examination of exposure through drinking water for all registered uses of chlorpyrifos" Drinking Water Assessment at 12.

As the current assessment stands, it is insufficient for final regulatory decision-making and can only be viewed as a preliminary, screening-level step. In order to evaluate exposure for input into aggregate human health assessment, continued EPA work is required at the very least to refine the assessment using the data already available to the Agency and to allow the assessment to move beyond its current realm of speculation and unsupported conclusions. Ultimately, a wholesale rethinking of the exposure assessment paradigm is sorely needed through the development of an appropriate assessment framework that more realistically represents the agricultural landscape and drinking water resources. This would allow the Agency to execute useful drinking water exposure assessments that would result in defensible science-driven regulatory decisions.

E. EPA's Drinking Water Assessment Warrants SAP Review.

EPA's refined drinking water assessment for chlorpyrifos is based upon the Agency's standard IR formulation, which has been in use as a screening-level tool since the late 1980s, and which has not been reviewed by a SAP since 1988. Thus, EPA's assessment does not consider many options for refinement that have been proposed specifically for chlorpyrifos by DAS and several experts during previous comment periods and in DAS's study submitted to EPA in early 2016. Refinements have also been proposed through scientific conferences, Environmental Modeling Public Meeting presentations and through CLA. EPA's failure to consider these approaches to refinement warrants independent review. EPA should bring these refinement techniques to a SAP and seek guidance on how to make their assessments reflect the best available science before using an approach that was last reviewed eighteen years ago.

EPA attempts to make the current assessment appear probabilistic in nature by simulating different crops; however, the results are all considered to be equally probable and are all cases

that "could happen" by assuming that an entire drinking water source watershed contains the crop (100% Percent Cropped Area ("PCA") and that the entire area is treated on a single day at worst-case application rates and timings. Indeed, within the IR methodology, a PCA of <100% is recommended as a refinement and EPA has published guidance on developing PCAs for major crops and some common combinations of two crops.[12] However, for a product such as chlorpyrifos, with many crop uses potentially occurring in the same watershed but with different cropping management practices and application rates and timing, the PCA methodology in the EPA's 2014 guidance is insufficient; it is necessary to bring more detailed and available cropping intensity data into the analysis to truly refine the assessment. This point was noted in the 2014 PCA guidance, which recommended the use of the USDA National Agricultural Statistics Service Cropland Data Layer ("CDL") as a data source. Such an approach was submitted to EPA by DAS in February 2016 following discussions with the Agency in a meeting with EFED in September 2015 (September 2015 EPA Meeting, EPA-HQ-OPP-2008-0850-0853). The DAS submission offered a pragmatic and still conservative consideration of PCA that resulted in a significant refinement of modeled drinking water estimates.

In addition, EPA performed some preliminary analysis of a nationwide (but not publicly-available) database of validated drinking water watersheds and intakes that could aid in identifying drinking water sources at potential risk from pesticides. However, the Agency did not apply any results of the analysis in the current assessment, because of perceived incompleteness or uncertainties in that database. The potential degree of over-estimation of exposures due to this lack of refinement and recommendations on appropriate use of best methodologies and available approaches further warrant independent SAP review.

References:

Bohaty RFH, Revised Chlorpyrifos Preliminary Registration Review Drinking Water Assessment, EPA-HQ-OPP-2008-0850-0026 (June 20, 2011)

Bohaty RFH, Chlorpyrifos: Updated Drinking Water Assessment for Registration Review, EPA-HQ-OPP-2008-0850-0198 (Dec. 23, 2014)

[12] EPA, *Development of Community Water System Drinking Water Intake Percent Cropped Area Adjustment Factors for use in Drinking Water Exposure Assessments: 2014 Update,* https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/development-community-water-system-drinking-water.

Bohaty RFH, Hetrick J., Chlorpyrifos Refined Drinking Water Assessment for Registration Review, EPA-HQ-OPP-2015-0653-0437 (Apr. 14, 2016)

Chen W, Hertl P, Chen S, Tierney D (2002). A pesticide surface water mobility index and its relationship with concentrations in agricultural drainage watersheds. Environ. Toxicol. Chem. 21:298–308

Helsel DR (2005) *Nondetects and Data Analysis: Statistics for Censored Environmental Data.* John Wiley & Sons. Hoboken, New Jersey

Jones RD, Able S, Effland W, Matzner R, Parker R (1998) An Index Reservoir for use in Assessing Drinking Water Exposures. Presentation given at the FIFRA Science Advisory Panel *Proposed Methods for Basin-scale Estimation of Pesticide Concentrations in Flowing Water and Reservoirs for Tolerance Reassessment*, July 29-30, 1998.

Mosquin PL, Aldworth J, Poletika, NN (2015). Peak centiles of chlorpyrifos surface-water concentrations in the NAWQA and NASQAN programs. *Water Research* 69:261-273

Oliver G, Juberg D, Burns C, Bartels M, Velovitch J, Poletika N, Khoshab A, Racke K, Martin D, Felming C, Richardson J (2015) Dow AgroSciences LLC's Response to EPA's Revised Human Health Risk Assessment for Chlorpyrifos Registration Review – EPA-HQ-OPP-0850-0224; Dow AgroSciences Study ID GR 4302105, 29-April-2015; regulations.gov docket reference EPA-HQ-OPP-0850-0845, posted 9-June-2015.

Perkins, DB; Jones, K; Amos, JJ; Snyder, NJ; Wright, KN; Guth, N (2016) Chlorpyrifos: Preliminary National-scale Refined Drinking Water Exposure Assessment; Unpublished study of Dow AgroSciences, performed by Waterborne Environmental, Inc. DAS study ID 151193, 19-Feb-2016. MRID 50016001.

Reiss, R (2015) A review of EPA's Drinking Water Exposure Assessment for Chlorpyrifos. Report of Exponent, Inc. for Dow AgroSciences; 28-April-2015; regulations.gov docket reference EPA-HQ-OPP-2008-0850-0792.

Solomon, KR, Williams WM, Mackay D, Purdy J, Giddings JM, Giesy JP (2014). Properties and Uses of Chlorpyrifos in the United States. *Rev Environ Contam Toxicol* **231**: 13-34

Stone WW, Crawford CG, Gilliom RJ (2013). Watershed Regressions for Pesticides (WARP) Models for Predicting Stream Concentrations of Multiple Pesticides. *J Environ Qual* 42:1838–1851.

EPA, Guidance on the Development, Evaluation, and Application of Environmental Models (Mar. 2009).

EPA, Development of Community Water System Drinking Water Intake Percent Cropped Area Adjustment Factors for use in Drinking Water Exposure Assessments: 2014 Update. Environmental Fate and Effects Division, Office of Chemical Safety and Pollution Prevention.

9-September-2104, https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/development-community-water-system-drinking-water (accessed Jan. 5, 2017).

EPA, Meeting between Dow AgroSciences (DAS) and EPA where DAS presented eight actionable concepts for refining predictions of surface water concentrations, EPA-HQ-OPP-2008-0850-0853 (Sept. 2015).

EPA, Biological Evaluation Chapters for Chlorpyrifos ESA Assessment; Attachment 1-3, "Method for Established the Use Site Footprint" https://www3.epa.gov/pesticides/nas/attachment-1-3.docx, (accessed Jan. 3, 2017).

XII. EPA's Proposed Revocation of Tolerances Should be Considered a Significant Regulatory Action.

EPA assessments underestimate the economic impact of revocation of chlorpyrifos tolerances. U.S. growers and farmers have expressed the critical need for and value of chlorpyrifos in previous and current comments, which EPA has not recognized in its current assessments. EPA's proposed revocation of tolerances will impact U.S. growers, many of them small family farms, along with food processors and distribution companies. It will also negatively affect global trade of key consumer-important crops and crop products into the United States. When combined, the economic impact could easily make the proposed revocation of tolerances a significant regulatory action.

A. EPA's Proposed Revocation of Tolerances Does Not Accurately Consider the Economic Impact to U.S. Agriculture.

EPA's NODA and accompanying assessments do not include an update or full evaluation of the important production and economic impacts of the proposed tolerance revocations. The only economic evaluation appears to be the EPA Analysis of the Small Business Impact of Revoking Chlorpyrifos Food Tolerance from 2015 (USEPA, 2015). This analysis was challenged in comments by DAS previously submitted to the docket in 2016 (Oliver et al. 2016). In addition, a study of the benefits of chlorpyrifos to U.S. growers was also submitted to the docket in 2016 (Nelson and Schneider, 2016b). Neither has been responded to by EPA or considered in the NODA.

U.S. agriculture recognizes the impact of the proposed revocation of tolerances, which would effectively cause the loss of their uses of chlorpyrifos. Twenty-three hundred (2,300) U.S. growers, many of them representing family farms, have expressed their need for chlorpyrifos on the critical crops of corn, soybean, wheat, cotton, alfalfa, and sugar beets, along with multiple

other crops through petitions submitted to the current docket. EPA-HQ-OPP-2015-0653. In addition, multiple grower groups have provided comments expressing the need for chlorpyrifos in previous and the current comment periods. Oliver et al. (2016) identified several failings of the EPA's analysis of Small Business Impact which cause a significant underestimation of the potential impact:

- The focus only on control of primary pests fails to fully account for all reasons a grower needs chlorpyrifos. These other documented reasons should be considered rather than being dismissed as "uncertainties" and then not evaluated as in the current assessment.

- The impact in particular regions can be expected to be more severe than shown in EPA's national-level assessment. EPA's conclusion that even in these regions "relatively few additional farms may be impacted" is unsupported by the evidence presented. Region-specific assessments are needed.

Chlorpyrifos contributes significantly to the control of insect pests in a wide range of corps including cereal, oil, forage, fruit, nut, and vegetable crops. In some situations, it is the only tool growers have for controlling a serious pest and maintaining their profitability. A more complete analysis of the value of chlorpyrifos shows there are many reasons growers rely on chlorpyrifos (Nelson and Schneider, 2016b):

- Reliable control of a broad spectrum of insect pests;

- Active on foliar-feeding and soil-dwelling insect pests;

- Fast knockdown;

- Significantly less disruptive to beneficial populations than some other insecticides and does not flare mites or aphids;

- Flexible application timing and method;

- Important tank mix partner for controlling tough pests;

- Good rotational partner to manage insect resistance;

- Easily implemented into existing IPM and IRM programs;

- Excellent safety on the crop;

- Broad label;

- International tolerances and maximum residue limits in place in export destination countries;
- Moderate mammalian toxicity;
- Easy to handle; and
- Strong technical support database

Each of the attributes listed above carries an economic value for the individual grower, and therefore each also carries an economic impact if tolerances for chlorpyrifos are revoked.

B. Revocation of Tolerances Will Have Significant Negative Impacts on Trade.

Today, chlorpyrifos is registered in about 100 countries for use on more than fifty different crops against damage caused by a wide-range of insect pests. Revoking chlorpyrifos tolerances would result in significant disruption in the pest management practices used in the production of certain import crops, disruption of long-standing trade relationships, and create a new set of winners and losers as market participants adapt to regulatory changes. This represents a significant impact on trade with particular relevance to developing countries that rely on exports of agricultural commodities to the United States (Nelson and Schneider, 2016a).

In an assessment focused on chlorpyrifos use on key crops exported to the United States from several important trading partners, including Brazil, Canada, Costa Rica, Israel, Mexico, Morocco, South Africa, and Spain, Nelson and Schneider (2016) reported potentially significant economic impact from both the perspective of consumers and food chain members in the United States and also from the perspective of the exporting countries:

- Citrus fruit and essential oils of citrus (Mexico), wine (Italy), and soybeans (Brazil) are the U.S. imports most impacted by revoking chlorpyrifos' tolerances because of the large proportion of each commodity imported from these countries and the large crop area treated with chlorpyrifos.
- From the export partners' perspective, citrus fruit and essential oils of citrus (Mexico), wine (Italy), soybeans (Brazil), essential oils of citrus (Israel, South Africa, Spain), sorghum (Mexico), and sugar (Costa Rica) are the exports most impacted by revoking chlorpyrifos' tolerances because of the large proportion of each commodity exported from these countries to the U.S. and the large crop area treated with chlorpyrifos.

References

Nelson, J.E., Schneider, L.L. 2016a. The Impact of Revoking Chlorpyrifos Tolerances (MRLs) on U.S. Agricultural Imports from Key Food Exporting Countries. Nelson-Schneider Consulting LLC. Submitted to docket: EPA-HQ-OPP-2015-0653, January 2017.

Nelson, J.E., Schneider, L.L. 2016b. Use and Benefits of Chlorpyrifos in Agriculture. Nelson-Schneider Consulting LLC. Submitted to docket EPA-HQ-2015-0653, January 2016.

Oliver, G., Poletika, N., Burns, C., Juberg, D., Hastings, K., Velovitch, J., Richardson, J., Racke, K., Bartels, M., Marty, S. 2016. Dow AgroSciences Response to EPA's: Chlorpyrifos; Tolerance Revocations; Proposed Rule and EPA Analysis of the Small Business Impacts of Revoking Chlorpyrifos Food Tolerances at 126. EPA-HQ-OPP-2015-0653-0386.

EPA, Analysis of the Small Business Impact of Revoking Chlorpyrifos Food Tolerances, EPA-HQ-OPP-2015-0653-002 (Oct. 27, 2015).

XIII. Principles of Sound Science and Good Government Warrant that EPA Must Deny the Petition and Convene the SAP to Review the RHHRA and 2016 Drinking Water Assessment for Chlorpyrifos.

EPA appears to be exploiting a court-imposed deadline while sacrificing science, objectivity, and the Agency's own credibility to achieve its desired regulatory policy goals. EPA should immediately deny the Petition and convene the SAP to review the RHHRA and 2016 drinking water assessment for chlorpyrifos. After taking guidance from the SAP on these important issues, the Agency must complete Registration Review pursuant to FIFRA and address the issues raised herein and in the additional comments to the chlorpyrifos docket raised by DAS and other stakeholders before taking final action with respect to chlorpyrifos. Registration Review will allow the Agency to complete its assessment of chlorpyrifos in a thorough, science-based manner in keeping with the Agency's statutory mandates. Completing Registration Review would go a long way toward restoring the transparency in the regulatory process for chlorpyrifos that has been sorely lacking since EPA's abrupt shift in policy in 2015.

Appendix A

Prior DAS Comments and Other Submissions to EPA that Should be Considered by the Agency

1. Edwards, D., Juberg, D., Burns, C., Goodman, J., Li, A., Bartels, M., Lickfeldt, D. (2013). Epidemiology Studies Pertaining to Chlorpyrifos Exposures: Consideration of Reliability and Utility. Submitted by Dow AgroSciences to EPA November 12, 2013. (EPA-HQ-OPP-2008-0850-0511; EPA-HQ-OPP-2015-0653-0201).

2. Poet, T.S. (2015). Multi-Route, Lifestage, and Pregnancy PBPK/PD model for Chlorpyrifos and Chlorpyrifos-Oxon: Model development and validation. A report of the Summit Toxicology Group, dated April 2015. (EPA-HQ-OPP-2008-0850-0514).

3. Reiss, R. (2015). Review of EPA's Occupational and Residential Exposure Assessment for Chlorpyrifos. Exponent. Project Identification 1500180.000, dated April 2015 (submitted to docket: EPA-HQ-2008-0850).

4. Gradient's Comments on the EPA's Revised Human Health Risk Assessment of Chlorpyrifos, dated April 24, 2015. (EPA-HQ-OPP-2008-0850-0508).

5. Mosquin, P.L., Aldworth, J. (2015), A Review of the Updated Chlorpyrifos Drinking Water Assessment. Technical Report of RTI International, dated April 28, 2015. (EPA-HQ-OPP-2008-0850-0551; EPA-HQ-OPP-2015-0653-0053).

6. Oliver, G., Juberg, D., Burns, C., Bartels, M., Velovitch, J., Poletika, N., Khoshab, A., Racke, K., Martin, D., Felming, C., Richardson, J. (2015). Dow AgroSciences LLC's Response to EPA's Revised Human Health Risk Assessment for Chlorpyrifos Registration Review, dated April 29, 2015. (EPA-HQ-OPP-2008-0850-0845; EPA-HQ-OPP-2015-0653-0214).

7. Oliver, G., Juberg, D., Burns, C., Bartels, M., Marty, S., Velovitch, J. Khoshab, A., Hastings, K., Racke, K., Dow AgroSciences LLC's Response to EPA's Chlorpyrifos-Methyl: Human Health *Draft* Risk Assessment ("DRA") for Registration Review, dated November 18, 2015. (EPA-HQ-OPP-2010-0119-0044).

8. Burns, C. (2015). Comments on EPA's Literature Review on Neurodevelopment Effects & FQPA Safety Factor Determination for the Organophosphate Pesticides, dated December 22, 2015 (EPA-HQ-OPP-2010-0119-0045; EPA-HQ-OPP-2015-0653-0230).

9. Reiss, R. (2015). A Review of EPA's Drinking Water Exposure Assessment for Chlorpyrifos, dated April 28, 2015. (EPA-HQ-OPP-2008-0850-0792; resubmitted to docket: EPA-HQ-OPP-2015-0653).

10. Marty, M. S., Marshall, V. A. (2014). Characterization of Cholinesterase (ChE) Inhibition Following Acute Exposure to Chlorpyrifos-Oxon ("CPFO") in Drinking Water. A report of The Dow Chemical Company (submitted to EPA in 2015).

11. Nelson, J.E., Schneider, L.L. (2016b). Use and Benefits of Chlorpyrifos in Agriculture. Nelson-Schneider Consulting LLC, dated January 4, 2016. (EPA-HQ-OPP-2015-0653-0227).

12. Oliver, G., Poletika, N., Burns, C., Juberg, D., Hastings, K., Velovitch, J., Richardson, J., Racke, K., Bartels, M., Marty, S. (2016). Dow AgroSciences Response to EPA's: Chlorpyrifos; Tolerance Revocations; Proposed Rule and EPA Analysis of the Small Business Impacts of Revoking Chlorpyrifos Food Tolerances, dated January 4, 2016. (EPA-HQ-OPP-2015-0653-0386).

13. Oliver, G., Dow AgroSciences Legal and Policy Comments in Response to EPA's Proposed Rule to Revoke Tolerances for Chlorpyrifos, dated January 5, 2016. (EPA-HQ-OPP-2015-0653-0266).

14. Oliver, G., Dow AgroSciences LLC's Legal and Policy Comments in Response to (i) EPA's Literature Review on Neurodevelopment Effects & FQPA Safety Factor Determination for the Organophosphate Pesticides and (ii) EPA's Chlorpyrifos-Methyl: Human Health Draft Risk Assessment for Registration Review, dated February 19, 2016. (EPA-HQ-OPP-2010-0119-0033).

15. Perkins, D.B.; Jones, K.; Amos, J.J.; Snyder, N.J.; Wright, K.N.; Guth, N. (2016) Chlorpyrifos: Preliminary National-scale Refined Drinking Water Exposure Assessment; Unpublished study of Dow AgroSciences, performed by Waterborne Environmental, Inc. DAS study ID 151193, 19-Feb-2016. MRID 50016001.

16. Dow AgroSciences LLC's Request for EPA to (i) Explain its Reliance on Epidemiology Studies in the Face of Incomplete and Insufficient Underlying Raw Data and (ii) Reopen the Comment Periods for EPA's Revised Human Health Risk Assessment for Chlorpyrifos and Proposed Rule to Revoke all Chlorpyrifos Tolerances, dated March 30, 2016. (EPA-HQ-OPP-2016-0062-0107).

17. Dow AgroSciences LLC's Petition to Postpone the April 2016 FIFRA SAP, dated April 4, 2016. (EPA-HQ-OPP-2016-0062-0106).

18. Initial Comments by Dow AgroSciences LLC to the Scientific Advisory Panel, dated April 8, 2016. (EPA-HQ-OPP-2016-0062-0110).

19. Dow AgroSciences Additional Comments for the EPA's FIFRA Scientific Advisory Panel ("SAP"): Chlorpyrifos: Analysis of Biomonitoring Data (April 19-21), dated April 15, 2016. (EPA-HQ-OPP-2016-0062-0123).

20. Driver, J., Ross, J., Comments to Chlorpyrifos Issue Paper: Evaluation of Biomonitoring Data from Epidemiology Studies, dated April 16, 2016. (submitted to docket: EPA-HQ-OPP-2016-0062).

21. Nelson, J.E., Schneider, L.L. (2016a), The Impact of Revoking Chlorpyrifos Tolerances (MRLs) on U.S. Agricultural Imports from Key Food Exporting Countries. Nelson-Schneider Consulting LLC, dated January 2017. (submitted to docket: EPA-HQ-OPP-2015-0653).

Appendix B

Deficiencies in the Columbia Study for Purposes of Risk Assessment

1. Raw data from the Columbia Study have been repeatedly requested but not made available.

EPA requires registrants submitting studies to the Agency to provide access to all data files supporting the studies. The raw data permit EPA to validate published analyses and conduct additional analyses not addressed in publications. Despite EPA's repeated requests, the Columbia study investigators have declined to share any data elements. Access to these data would permit additional analyses not addressed in the publications.

Essentially the Columbia study's cord blood and maternal blood data would form the primary exposure metric for their chlorpyrifos-related publications. These values and simple demographic data such as age, race, ethnicity and weight of the mother could ethically be shared without revealing identifying information about the study participants. A number of questions could be addressed with these data. For example, what is the influence of blood lipids upon the chlorpyrifos concentration in blood as recommended by Needham of the CDC (Needham 2005) To what degree does time from delivery to collection of maternal blood change exposure. (SAP Tr. at 485) What are the comparisons between paired cord and maternal data, not just the overall correlations. *Id.* at 487.

2. Spot samples as collected in the Columbia Study at delivery are insufficient to determine exposure *in utero*.

The cord blood and maternal blood chlorpyrifos concentrations used in the Columbia publications for neurodevelopment effects are based upon a single measurement. The maternal samples were collected at or near delivery. The 2016 SAP members stressed that a sample collected at delivery would not adequately reflect the internal dose during gestation. SAP Tr. at 567 ("The reliance on a single cord blood measurement from only one study, *i.e.,* the Columbia study, as the primary basis for a highly impactful regulatory decision appears to go against standard practices of science in the field of toxicology and pharmacology."). Similarly, Needham (2005) said that sampling should have been timed before and after a chlorpyrifos application to better capture the range of exposure. Multiple publications have highlighted the intra- and inter-individual variability of short-lived chemicals and the potential for misclassification of exposure when using a single sample (*e.g.,* Aylward et al. 2014; Bradman and Whyatt et al. 2005; LaKind

et al. 2014). Notably, the maternal blood chlorpyrifos concentrations were not correlated with the personal air samples when collected more than a month from delivery (Spearman rank = 0.09) (Whyatt et al. 2003). While chlorpyrifos in blood is specific to the parent insecticide, as opposed to a metabolite in urine, the use of a spot sample from the Columbia Study does not adequately demonstrate that the biomarker is representative of longer term exposures.

3. The "high" dose level of >6.17 pg/g was arbitrarily determined and not biologically relevant.

As described in Rauh et al. (2006), chlorpyrifos levels were categorized into 4 groups: undetectable levels (n=80) and three tertiles based on detectable values (tertile 1 (n=65); tertile 2 (n=39); tertile 3 (n=44)). The authors noted that "in preliminary analyses, we found no indication of either a linear or nonlinear dose-response relationship between chlorpyrifos levels and developmental outcomes." The authors then based all future analyses upon a dichotomized variable with a cut-point value of 6.17 pg/g.

i. The highest exposure group, tertile 3 (> 6.17 pg/g), was based only upon the concentration range from the analyzed sample of children. The groups were constructed from the distribution (nondetectable and equal tertiles) of the samples collected in the Columbia cohort. However, this distribution is poorly defined and each published analysis featured different numbers of children. For example, the sample size in analyses of birth outcomes ranged from 263 to 314 (Perera et al. 2003; Whyatt et al. 2004). At age 3, the reported number of children for analyses was 254, 266 and 348 (Horton et al. 2011; Lovasi et al. 2011; Rauh et al. 2006) and the number was 265 at age 7 (Rauh et al. 2011). It is not clear from the publications on newborns (n = 263 to 314) what value defined the upper tertile. The cut point of "6.17" was not introduced until the children were ages 1 – 3 years of age (Rauh et al. 2006). Notably, access to the raw data would permit better understanding of the distribution of chlorpyrifos concentrations across the cohort children and the resulting cut point of the upper tertile.

ii. The value of 6.17 pg/g is well below chlorpyrifos concentrations expected to inhibit cholinesterase. Butyl cholinesterase and red blood cell (RBC) cholinesterase inhibition are well established indicators of exposure in occupationally exposed populations. Two studies independently reported an inflection point for observation of butyl cholinesterase inhibition at an estimated dose of 5 µg/kg/day (Farahat et al. 2011; Garabrant et al. 2009). The value of 5 µg/kg/day is several-fold higher than the estimated maximum daily intake of 0.077 µg/kg/day for

the Columbia Study infants based on modeling of the cord blood and personal air monitoring data (Eaton et al. 2008).

iii. A better approach would be to create three exposed groups. The three groups below 6.17 pg/g were combined and defined as the Low exposure group (including the undetectable levels). Combining the undetectable group with those who have low chlorpyrifos exposure may not have been appropriate. The undetectable group may have inherent differences than three tertiles with detectable chlorpyrifos exposure. In combining the three groups as "low" the authors precluded the ability to confirm or refute any dose-response relationships.

iv. The "high" chlorpyrifos concentration of 6.17 pg/g, was well below the limit of quantitation of 15 pg/g. The quantitation of chlorpyrifos in maternal and umbilical cord blood was conducted at the U.S. CDC laboratory utilizing the published analytical method of Barr et al. (2002). The authors of the analytical method used for these assays defined the limit of detection (LOD) for chlorpyrifos as 1 pg/g serum. Current bioanalytical method validation criteria call for preparation of replicate fortified matrix ("QC spike") samples at the limit of quantitation, to verify accurate determination of analyte concentrations across the range of concentrations expected in a sample set. However, no QC spikes were reported to be prepared at the stated LOD of 1 pg/g serum during the conduct of these exposure studies. Analyte recoveries were reported in the manuscript for QC spikes at 15 and 50 pg/g serum, showing adequate results down to the concentration of 15 pg/g. Based on these criteria requirements and validation results, the validated Limit of Quantitation (LOQ) for measurement of chlorpyrifos in serum by this method should be set at 15 pg/g. Most of the Columbia Study samples were below the fully validated LOQ of 15 pg/g serum. Thus, the statistical differences between the "low" and "high" subgroups may not be valid.

4. Other potential confounders and effect modifiers were unmeasured.

The tests scores may be confounded by language. The Bayley test performance is not designed for children whose first language is not English. Rauh et al. (2006) reported Black children scored higher than Dominican children on the Bayley test. While a larger number of the mothers were Dominican (58%) than African American (Whyatt et al. 2004), the percentage of Dominican mothers who spoke Spanish as a first language was not provided. Therefore, infants raised in Spanish-speaking households may be at a disadvantage for Bayley testing assessment.

Additionally, language may lead to higher pesticide exposure among children due to a parent's inability to read pesticide label instructions written in English. Thus, language, more than race/ethnicity, may be an important uncontrolled confounder, associated with both poor performance on test scores and higher chlorpyrifos levels.

Based on standardized testing, about a third of the children in the study were experiencing cognitive and psychomotor developmental delay by age 3, regardless of whether they had detectable chlorpyrifos exposure. This suggests that, apart from chlorpyrifos, other factors are important in this population. Influences during childhood, such as maternal depression, nutritional deficiencies, and living in settings of violence and drug abuse can also lead to developmental delays. Conversely, positive parental activities as simple as reading aloud have been shown to improve test scores. None of these was reported by the Columbia Study. Further, many of the factors related to reasons for using insecticides in the home (*e.g.*, cockroach infestation associated with poor housing maintenance, hygiene, and care environment) may also be determinants of lower test performance.

5. The limitations in epidemiology studies should be quantified before creating "uncertainties" for use in risk assessment.

The "uncertainty" for risk assessors occurs when applying the results from animal or in vitro studies to humans. Viewed as a data gap, the uncertainty can be reduced by increasing the amount, quality, consistency and relevance of evidence particularly for data between species. In contrast, uncertainty in epidemiology studies pertains to random error and systematic error (i.e., bias). This uncertainty is more about the validity of a study's findings than the its applicability to other populations. A weak epidemiology study may have faulty conclusions. The impact of study limitations is rarely quantified and is often dismissed (Greenland and Gustafson 2006; Jurek et al. 2008; Thomas 1995). A workshop of more than 30 epidemiologists and toxicologists from industry, academia and government recommended that epidemiologists should improve efforts to validate exposure and quantify uncertainty in their studies (Burns et al. 2014).

In conclusion, while the Columbia Study utilized a high quality prospective design, it has substantial weaknesses that preclude its use in risk assessment. Importantly, sampling of the maternal and cord blood was conducted only once and was not timed with a chlorpyrifos application. Exposure during the pregnancy, which would be more etiologically relevant, was not measured. Many risk factors for neurodevelopment were not controlled by the study

investigators. Limitations in data analyses and exposure assessment is common in observational epidemiology studies. Thus, no one epidemiology study is sufficiently robust for use in formal risk assessment. A list of elements as proposed by Hill are a common tool but using more sophisticated analytical approaches for individual studies is also recommended (Burns et al. 2014).

References.

Aylward, L.L., Hays, S.M., Smolders, R., Koch, H.M., Cocker, J., Jones, K., Warren, N., Levy, L., and Bevan, R. 2014. Sources of variability in biomarker concentrations. J Toxicol Environ Health B Crit Rev **17**(1): 45-61. doi: 10.1080/10937404.2013.864250.

Barr, D.B., Barr, J.R., Maggio, V.L., Whitehead, R.D., Sadowski, M.A., Whyatt, R.M., and Needham, L.L. 2002. A multi-analyte method for the quantification of contemporary pesticides in human serum and plasma using high-resolution mass spectrometry. J Chromatogr B Analyt Technol Biomed Life Sci **778**(1-2): 99-111.

Bradman, A., and Whyatt, R.M. 2005. Characterizing exposures to nonpersistent pesticides during pregnancy and early childhood in the National Children's Study: a review of monitoring and measurement methodologies. Environ Health Perspect **113**(8): 1092-1099.

Burns, C.J., Wright, J.M., Pierson, J.B., Bateson, T.F., Burstyn, I., Goldstein, D.A., Klaunig, J.E., Luben, T.J., Mihlan, G., Ritter, L., Schnatter, A.R., Symons, J.M., and Yi, K.D. 2014. Evaluating uncertainty to strengthen epidemiologic data for use in human health risk assessments. Environ Health Perspect **122**(11): 1160-1165. doi: 10.1289/ehp.1308062.

Eaton, D.L., Daroff, R.B., Autrup, H., Bridges, J., Buffler, P., Costa, L.G., Coyle, J., McKhann, G., Mobley, W.C., Nadel, L., Neubert, D., Schulte-Hermann, R., and Spencer, P.S. 2008. Review of the toxicology of chlorpyrifos with an emphasis on human exposure and neurodevelopment. Crit Rev Toxicol **38 Suppl 2**: 1-125. doi: 10.1080/10408440802272158.

Farahat, F.M., Ellison, C.A., Bonner, M.R., McGarrigle, B.P., Crane, A.L., Fenske, R.A., Lasarev, M.R., Rohlman, D.S., Anger, W.K., Lein, P.J., and Olson, J.R. 2011. Biomarkers of chlorpyrifos exposure and effect in Egyptian cotton field workers. Environ Health Perspect **119**(6): 801-806. doi: 10.1289/ehp.1002873.

Garabrant, D.H., Aylward, L.L., Berent, S., Chen, Q., Timchalk, C., Burns, C.J., Hays, S.M., and Albers, J.W. 2009. Cholinesterase inhibition in chlorpyrifos workers: Characterization of biomarkers of exposure and response in relation to urinary TCPy. J Expo Sci Environ Epidemiol **19**(7): 634-642. doi: 10.1038/jes.2008.51.

Greenland, S., and Gustafson, P. 2006. Accounting for independent nondifferential misclassification does not increase certainty that an observed association is in the correct direction. Am J Epidemiol **164**(1): 63-68. doi: 10.1093/aje/kwj155.

Horton, M.K., Rundle, A., Camann, D.E., Boyd Barr, D., Rauh, V.A., and Whyatt, R.M. 2011. Impact of prenatal exposure to piperonyl butoxide and permethrin on 36-month neurodevelopment. Pediatrics **127**(3): e699-706. doi: 10.1542/peds.2010-0133.

Jurek, A.M., Greenland, S., and Maldonado, G. 2008. How far from non-differential does exposure or disease misclassification have to be to bias measures of association away from the null? Int J Epidemiol **37**(2): 382-385. doi: 10.1093/ije/dym291.

LaKind, J.S., Sobus, J.R., Goodman, M., Barr, D.B., Fürst, P., Albertini, R.J., Arbuckle, T.E., Schoeters, G., Tan, Y.M., Teeguarden, J., Tornero-Velez, R., and Weisel, C.P. 2014. A proposal for assessing study quality: Biomonitoring, Environmental Epidemiology, and Short-lived Chemicals (BEES-C) instrument. Environ Int **73**: 195-207. doi: 10.1016/j.envint.2014.07.011.

Lovasi, G.S., Quinn, J.W., Rauh, V.A., Perera, F.P., Andrews, H.F., Garfinkel, R., Hoepner, L., Whyatt, R., and Rundle, A. 2011. Chlorpyrifos exposure and urban residential environment characteristics as determinants of early childhood neurodevelopment. Am J Public Health **101**(1): 63-70. doi: 10.2105/AJPH.2009.168419.

Needham, L.L. 2005. Assessing Exposure to Organophosphorus Pesticides by Biomonitoring in Epidemiologic Studies of Birth Outcomes. Environmental Health Perspectives **113**(4): 494-498. doi: 10.1289/ehp.7490.

Perera, F.P., Rauh, V., Tsai, W.Y., Kinney, P., Camann, D., Barr, D., Bernert, T., Garfinkel, R., Tu, Y.H., Diaz, D., Dietrich, J., and Whyatt, R.M. 2003. Effects of transplacental exposure to environmental pollutants on birth outcomes in a multiethnic population. Environ Health Perspect **111**(2): 201-205.

Rauh, V., Arunajadai, S., Horton, M., Perera, F., Hoepner, L., Barr, D.B., and Whyatt, R. 2011. Seven-year neurodevelopmental scores and prenatal exposure to chlorpyrifos, a common agricultural pesticide. Environ Health Perspect **119**(8): 1196-1201. doi: 10.1289/ehp.1003160.

Rauh, V.A., Garfinkel, R., Perera, F.P., Andrews, H.F., Hoepner, L., Barr, D.B., Whitehead, R., Tang, D., and Whyatt, R.W. 2006. Impact of prenatal chlorpyrifos exposure on neurodevelopment in the first 3 years of life among inner-city children. Pediatrics **118**(6): e1845-1859. doi: 10.1542/peds.2006-0338.

Thomas, D.C. 1995. Re: "When will nondifferential misclassification of an exposure preserve the direction of a trend?". Am J Epidemiol **142**(7): 782-784.

Whyatt, R.M., Camann, D., Perera, F.P., Rauh, V.A., Tang, D., Kinney, P.L., Garfinkel, R., Andrews, H., Hoepner, L., and Barr, D.B. 2005. Biomarkers in assessing residential insecticide exposures during pregnancy and effects on fetal growth. Toxicol Appl Pharmacol **206**(2): 246-254. doi: 10.1016/j.taap.2004.11.027.

Whyatt, R.M., Barr, D.B., Camann, D.E., Kinney, P.L., Barr, J.R., Andrews, H.F., Hoepner, L.A., Garfinkel, R., Hazi, Y., Reyes, A., Ramirez, J., Cosme, Y. and Perera, F.P. 2003 Environ Health Perspect **111**: 749-756.

Whyatt, R.M., Rauh, V., Barr, D.B., Camann, D.E., Andrews, H.F., Garfinkel, R., Hoepner, L.A., Diaz, D., Dietrich, J., Reyes, A., Tang, D., Kinney, P.L., and Perera, F.P. 2004. Prenatal insecticide exposures and birth weight and length among an urban minority cohort. Environ Health Perspect **112**(10): 1125-1132.

Appendix C

Requests for Raw Data and Expressions of Concern About Absence of Raw Data

- **July 16, 2012**: Dow AgroSciences LLC ("DAS") submits FOIA request to Environmental Protection Agency ("EPA") for raw data underlying Columbia Study (HQ-FOI-01618012).

- **September 17, 2012**: EPA denies DAS's FOIA request, claiming requested information is exempt from mandatory disclosure under FOIA Exemption 6 (Personal Information Affecting an Individual's Privacy).

- **October 16, 2012**: DAS submits FOIA appeal to EPA, asserting that request excluded information subject to protection under FOIA Exemption 6 (HQ-2012-03173-A, HQ-APP-2012-003392).

- **January 21, 2013**: EPA denies DAS's October 16, 2012 FOIA appeal because EPA did not possess any of the raw data requested.

- **January 25, 2013:** Letter from Steve Bradbury at EPA to Natural Resources Defense Council ("NRDC") and Pesticide Action Network North America ("PANNA"), stating that "[i]n order to complete both the dose reconstruction and analyses on other chemical exposures, however, we will need to analyze the original data ('raw data') from the Columbia University study to better understand the exposure to chlorpyrifos and other chemicals. To date, the study authors have declined our request to provide [the raw data] to us, but we are continuing to discuss our need for evaluating these data with the study authors and we are hopeful that a resolution can be reached."

- **December 23, 2014:** EPA's response to PANNA and NRDC's Renewed Petition for a Writ of Mandamus in the Ninth Circuit (No. 14-72794) states that "EPA's implementation of the Scientific Advisory Panel's recommendation to reconstruct and analyze the likely doses of chlorpyrifos that participants in a key epidemiological study were exposed to was delayed when the authors of the study refused to provide the raw data to EPA" and that "events such as EPA's inability to obtain raw data for an epidemiologic study . . . explain why EPA was unable to meet its previous prediction and highlight why a deadline would be impractical."

- **December 14, 2015**: DAS submits FOIA request seeking the raw data underlying the Columbia, Mt. Sinai and CHAMACOS Studies (EPA-HQ-2016-002089).

- **March 1 and 2, 2016**: EPA responds providing data files purportedly responsive to DAS's request.

- **March 31, 2016**: DAS submits FOIA appeal to EPA, stating that information provided was incomplete and nonresponsive, and that EPA had failed to request the data from the study investigators directly, as required under OMB Circular A-110 (EPA-HQ-2016-005270).

- **April 7, 2016:** EPA states, for the first time in response to "Petition by AMVAC to Postpone the Scheduled Meeting of the FIFRA Scientific Advisory Panel until the Panel Has Received and Reviewed All Underlying Data for the Columbia University Epidemiology Study" (March 29, 2016), that the raw data provided to DAS in response to its March 2016 FOIA request "does not represent the data presented by Columbia University investigators in their chlorpyrifos publications [and] were therefore deemed to be unusable."

- **April 19, 2016:** EPA formally requests raw data from Columbia researchers, observing that the Study was supported by federal grant funds and noting concerns with EPA's ability to "address our transparency goals as well as public feedback regarding access to the original ('raw') data."

- **April 2016:** The April 19-21, 2016 FIFRA Scientific Advisory Panel ("SAP") repeatedly expresses concern regarding the absence of the raw data. *See, e.g.,* SAP Tr. at 494 ("[N]ot having [raw] data was just amazing, flabbergasting."); *id.* at 495 ("I'm not sure that it's [. . .] clear to [me] why the data is not available.").

- **May 18, 2016:** Columbia rejects EPA's request for raw data, stating that disclosure of raw data would constitute an invasion of the privacy of the study participants.

- **June 22, 2016**: EPA responds to DAS's March 31, 2016 FOIA appeal, stating that EPA had provided DAS with data responsive to its FOIA request that it possessed, and that it had no possession or control of any additional data.

- **August 19, 2016**: DAS submits FOIA request for any and all raw data underlying Columbia Study (EPA-HQ-2016-009575).

- **September 19, 2016**: EPA responds to DAS's FOIA request, stating that agency had not yet reached an agreement with Columbia concerning the data for the epidemiology study.

Appendix D

Summary of Prior EPA and SAP Reviews of Robustness of Animal Toxicology Literature for Chlorpyrifos Relative to the Existing Regulatory Standard

Set forth below is the history relative to Agency and former SAP reviews on the robustness of the animal toxicology literature relative to (a) possible association between exposure to chlorpyrifos and neurodevelopmental/behavioral effects and (b) whether credible evidence exists suggesting that such effects occur below 10% RBC ChEI. One dominant theme over the past eight years during registration review of chlorpyrifos by both EPA and former SAPs is the experimental conditions in those studies reviewed, including (a) use of a neurotoxic solvent (DMSO) control during experimentation, (b) many studies in which cholinesterase inhibition was not measured (which challenges the contention that effects are occurring below 10% RBC ChEI), (c) in vitro studies that use doses that would be equivalent to in vivo exposures well above 10% RBC ChEI, (d) repetitive recognition over many years by both EPA and SAPs that no known mechanism of action exists to possibly explain suggested effects occurring below 10% RBC ChEI, and (e) the failure to recognize EPA-required, GLP scientific studies that demonstrate no neurodevelopmental effects at exposure levels that resulted in less than 10% RBC ChEI. Perhaps most significant is the fact that there is little new science from in vivo toxicology studies that conform to both previous SAP recommendations and to GLP-compliant designs to suggest that exposures corresponding to less than 10% RBC ChEI are associated with any effect, including neurodevelopmental effects, in animal studies. A review of both EPA and SAP publications/reviews during registration review demonstrate that there is little, if any evidence, that toxicological studies exist that convincingly show that neurodevelopmental effects exist from exposure that results in less than 10% RBC ChEI.

1. 2011 PHHRA

In its 2011 PHHRA, EPA states:

> [T]here is a growing body of literature [no citations provided by EPA] with laboratory animals, . . . indicating that gestational and/or early postnatal exposure to chlorpyrifos may cause persistent behavioral effects into adulthood….These behavioral effects are seen at doses that typically result in inhibition of ChE *in vivo*. Although there are several biological plausible hypotheses being investigated by researchers, the mode/mechanisms of action resulting in such effects are not known at this time.

PHHRA at 8.

2. 2012 EPA Issue Paper

In its 2012 Issue Paper, EPA describes in detail much of the literature (in vitro and in vivo) surrounding investigations into non-cholinergic effects from chlorpyrifos exposure, but repeatedly notes that in many of these studies, cholinesterase inhibition was not measured. DAS has previously commented to EPA on this critical element of experimental design, but to date, EPA has provided no response. Examples from the 2012 Issue Paper are as follows:

- "Cholinesterase activity was not measured." Issue Paper at 23.
- "Again, cholinesterase activity was not measured." *Id.* at 23.
- "In those experiments, however, neurite outgrowth is inferred from biochemical measurements and cholinesterase activity is not assessed concurrently." *Id.* at 24.
- "There was, however, no concurrent analysis of AChE inhibition in most of these studies." *Id.* at 30.

In summary of its review of the toxicological literature at the time (2012), the following statements were made by EPA relative to this literature:

- "Taken together, these data do not provide evidence for a specific profile of effects but instead suggest more global alterations in neurobehavioral function…. These studies have almost exclusively focused on doses that could produce some degree, however minimal, of AChE inhibition. Thus it is not be possible to know whether effects would be present at lower doses, since they have not been adequately studied." *Id.* at 52-53.
- "Moreover, historically, given the sensitivity of AChE inhibition data for OPs, these data have been considered to be protective of other potential toxicities and/or modes of action for OPs." *Id.* at 96.
- "This focus is consistent with the recommendation from the 2008 SAP that AChE data provide the most appropriate endpoint and dose-response data for deriving point of departure for purposes of risk assessment. Moreover, because of the Agency's long experience with assessing the potential risk to chlorpyrifos and other OPs, and because both the dose response approach based on AChE inhibition and also the exposure methodologies used in the 2011 assessment have been vetted by numerous SAPs, there is high confidence in those analyses." *Id*.
- "Experimental toxicology studies in rodents suggest that long-term effects from chlorpyrifos exposure may occur. Due to the dose selection in most of these in vivo studies evaluating effects such as behavior and cognition, it is not known whether such adverse effects would be shown at doses lower that those used for derivation of point of

departures. Despite this uncertainty . . . ChE inhibition is a sensitive and protective endpoint." *Id.* at 101.

- "The questions posed regards the nature and degree of uncertainty around points of departure based on 10% AChE inhibition to protect against neurodevelopmental outcomes. The database of in vivo animal toxicology neurodevelopmental studies on adverse outcomes includes only a small number of studies at or near the Agency's point of departure. Despite this uncertainty, the Agency's chronic oral point of departure is approximately 10-fold lower than doses used in repeated dosing studies. With respect to the mechanistic data, there are some effects which are similarly sensitive or more sensitive than AChE inhibition. The fact that there are, however, sparse data to support the in vitro to in vivo extrapolation, or the extrapolation from biological perturbation to adverse consequence significantly limits their quantitative use in risk assessment." *Id.* at 102.

3. 2012 SAP Response

In its review and response to the EPA Issue Paper, the SAP in 2012 noted the following:

> The Panel concurs with the Agency's position that AChE data continue to be the strongest resource of data for deriving points of departure for chlorpyrifos. The Panel's conclusion is based on the premise that all studies reporting neurobehavioral changes following *in vivo* prenatal or postnatal exposures to chlorpyrifos have been accompanied by AChE inhibition when measured at an appropriate time following administration of chlorpyrifos.
>
> The Panel additionally notes that studies evaluating neurodevelopmental effects entailed experimental designs that do not permit an efficient means of determining a point of departure for chlorpyrifos. Thus, just as . . . in the 2008 SAP, this Panel advises that the Agency continue to use AChE data at the most sensitive lifestages for dose-response analysis and deriving points of departure. Also in keeping with the 2008 SAP, this Panel expresses concern about the use of Dimethyl Sulfoxide (DMSO) as a vehicle because of its intrinsic toxicity, its potential influence on absorption and interaction with chlorpyrifos, and the impact of this interaction on the developing organism.
>
> Despite the issues raised by the Panel about these studies, the overall evidence across these studies is persuasive in indicating that there are enduring effects on the Central Nervous System (CNS) from chlorpyrifos exposure at or above 1.0 mg/kg. The Panel recommends that future neurodevelopmental studies be focused on testing chlorpyrifos levels below 1.0 mg/kg/day and that these studies be geared towards identifying the correct testing paradigm and neural substrates for detecting possible effects. The Panel advises that cross-laboratory or collaborative studies may provide systematic comparison of the effects of chlorpyrifos on neurodevelopmental domains using unified exposure periods, dosing, age of

testing, and methods, combined with urinary analysis of chlorpyrifos' metabolites, and accurate assessments of AChE inhibition.

2012 SAP Minutes at 12, 15.

4. 2014 RHHRA

It is well known and established that a dose level of 1 mg/kg/day in the rat is associated with significant inhibition of RBC ChE and the continued challenge is that most investigators fail to include in their experimental designs doses below this level. EPA continued to expound on the animal toxicological literature in its release of the 2014 RHHRA and commented that there is a lack of adequate investigation to support the contention that these various studies are convincingly demonstrating effects below 10% RBC ChEI. For example:

- "Overall, these data do not clearly show specific critical periods of exposure, or definitive sensitive behavioral outcomes. Unfortunately, no laboratory has provided systematic comparisons across exposure period, dosing regimen, and age of testing; such studies would improve understanding of the impact of these critical factors. These studies have almost exclusively focused on doses that could produce some degree, however minimal, of AChE inhibition . . . .Thus it is not possible to know whether effects would be present at lower doses, since they have not been adequately studied." RHHRA at 27.
- "Experimental toxicology studies in rodents suggest that long-term effects from chlorpyrifos exposure may occur. Due to the dose selection in most of these in vivo studies evaluating effects such as behavior and cognition, it is not known whether such adverse effects would be shown at doses lower than those which elicit 10% RBC AChE inhibition. It is notable, however, that comparing the lowest NOAEL observed in the in vivo animal studies (0.2 mg/kg/day; Billauer-Haimovitch et al. 2009) for the neurodevelopmental outcomes to the repeated dosing reliable BMDL10 ranging from 0.05-0.17 mg/kg/day for RBC AChE inhibition suggests that AChE inhibition is a sensitive endpoint." *Id.* at 45.

In its 2014 RHHRA, EPA again commented multiple times on the lack of inclusion of cholinesterase inhibition measurement within many of the toxicological studies. They note:

- "There was, however, no concurrent analysis of AChE inhibition in most of these studies." *Id.* at 153.
- "[T]here are, however, few papers that assessed concurrently the cholinesterase inhibition (either brain or blood) in those same animals. . . . It does appear, however, that most of the studies on the effects of chlorpyrifos on the serotonergic nervous system were conducted with doses of chlorpyrifos that likely produced marked inhibition of cholinesterase activity." *Id.* at 156.
- "In summary, in the late 2000s, a number of papers were published on the *in vitro* modification of various proteins by chlorpyrifos or chlorpyrifos oxon. Although

> interesting and provocative, these studies were usually conducted with exceedingly high concentrations . . . of the OP compound, making the connection to 'real world' human exposure tenuous." *Id.* at 158.

To provide one example where experimental design and treatment is critical relative to evaluation of effects at doses that do or do not cause cholinesterase inhibition, Johnson et al. (2009) reported the following in their Materials and Methods Section:

> The dosing regimen was designed to avoid OP-induced mortality and overt signs of toxicity but to maintain moderate levels of whole-brain inhibition throughout the exposure period. . . . It is unclear if these dosages are within the range of exposure levels in children. Most likely, CPS and MPS exposure in children will occur at levels lower than those used in this study with the exception of situation which involve high levels of contamination.

Frank O. Johnson, et al., *Developmental Chlorpyrifos and Methyl Parathion Exposure Alters Radial-Arm Maze Performance in Juvenile and Adult Rates*, Tox. Sci. 109(1). 132–142, at 133 (Mar. 12, 2009)

In summarizing much of the literature, EPA in 2014 concluded the following:

- "There continue to be inconsistencies in effects in relation to functional domains, dosing paradigms, and gender-specificity. The only studies reporting effects used doses that inhibited fetal/pup brain ChE activity to some degree, even though there were many negative effects at these same doses." RHHRA at 197.