Dow AgroSciences LLC's Response to Objections to EPA's Denial of Petition to Revoke All Tolerances and Cancel All Registrations for Chlorpyrifos

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I. INTRODUCTION

On March 29, 2017, the U.S. Environmental Protection Agency ("EPA" or the "Agency") issued an order denying an administrative petition (the "Petition") to revoke all tolerances and cancel all registrations for chlorpyrifos. EPA denied the Petition on the grounds that the scientific evidence was not sufficient to support the relief requested and required further study.

On June 5, 2017, Pesticide Action Network ("PAN")/Natural Resources Defense Council ("NRDC") *et al.* and the Attorneys General of the States of New York, Washington, California, Massachusetts, Maine, Maryland, and Vermont (individually "Petitioners" and collectively the "States"), and others, submitted objections to EPA's order denying the Petition (collectively the "Objections").[1] Dow AgroSciences LLC ("DAS") submits this Response to Objections in support of EPA's denial of the Petition and to clarify the scientific and factual record.

As set forth herein, EPA's Order correctly denied the Petition because there is an extensive and complete set of animal toxicology data that supports the current regulatory standard for chlorpyrifos. EPA's Order correctly recognized that its recent assessments and proposals with respect to chlorpyrifos were part of its non-binding agency deliberations and were based on inconclusive science that is not sufficient to support a change in the current regulatory standard for chlorpyrifos. The epidemiology and other studies advocated by the Petitioners are not reliable, consistent in their findings, nor valid for purposes of regulatory decision-making, and the Objections to the Order are otherwise meritless.

II. EXECUTIVE SUMMARY

For nearly fifty years, EPA has set a Point of Departure ("PoD") for chlorpyrifos based on cholinesterase inhibition.[2] This conservative and health-protective endpoint remains the gold standard used by regulatory bodies around the world, including the European Food Safety Authority ("EFSA") and the World Health Organization ("WHO"). Indeed, just over a year ago,

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[1] The District of Columbia joined in the States' objections on August 17, 2017.

[2] For chlorpyrifos, 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 inhibition ("RBC ChEI"). RBC ChEI 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.

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Australia concluded that "cholinesterase inhibition remains the most sensitive and relevant adverse effect caused by chlorpyrifos and is therefore the most appropriate endpoint for the establishment of health based guidance values used to protect the entire population including pregnant women, infants and children." Australian Pesticides and Veterinary Medicines Authority ("APVMA"), Reconsideration of Chlorpyrifos: Supplementary Toxicology Assessment Report at 1 (Apr. 2017) ("APVMA, Reconsideration of Chlorpyrifos"). Moreover, several Federal Insecticide, Fungicide, and Rodenticide Act ("FIFRA") Scientific Advisory Panels ("SAPs") convened by EPA over the past eight years have expressed confidence in RBC ChEI as the appropriate regulatory standard.

In 2006, EPA completed reregistration of chlorpyrifos under FIFRA and the Federal Food, Drug, and Cosmetic Act ("FFDCA") and reauthorized all existing agricultural uses for chlorpyrifos, relying on cholinesterase inhibition for the regulatory standard. This final decision and regulatory standard has been in effect ever since.

The current regulatory standard is supported by over fifty years of robust animal toxicological data generated during the statutorily mandated registration and reregistration review processes for chlorpyrifos. As discussed *infra,* Section V.A, EPA's 2011 Preliminary Human Health Risk Assessment ("PHHRA") stated that "[t]he toxicological database for chlorpyrifos is extensive and is adequate to support the registration review." EPA, Chlorpyrifos Preliminary Human Health Risk Assessment for Registration Review at 22 (June 30, 2011). EPA addressed the Food Quality Protection Act's ("FQPA") safety factor provision by relying on a robust set of animal toxicological data that accounted for children's susceptibility to set a safety factor of 1X in the Agency's 2006 cumulative risk assessment ("CRA") for organophosphate pesticides. *See* July 16, 2012 Letter from Steve Bradbury to PAN/NRDC ("2012 Bradbury Letter") at 20 ("Therefore, the Agency remains confident in the FQPA safety factor of 1X used in the cumulative risk assessment for chlorpyrifos.").

Contrary to Petitioners' claim, there is no credible, growing body of animal toxicology evidence corroborating the epidemiology studies claiming neurodevelopmental effects at exposure levels below the current regulatory standard. As detailed in DAS's prior comments and the attached Appendix A, animal toxicology studies examined by EPA and the California Department of Pesticide Regulation ("DPR") in their recent literature reviews and advanced by Petitioners and others as showing adverse neurodevelopmental outcomes suffer from significant

limitations, undermining the validity of their findings. For example, these studies employed doses at or above those known to result in 10% RBC ChEI or failed to measure cholinesterase inhibition at all, reported inconsistent findings, and/or had significant design flaws.

In addition, neither *in vitro* studies (*i.e.*, those studies conducted outside a living organism such as in a test tube or cell culture dish) nor epidemiology studies cited in the Petitioners' Objections create uncertainty with respect to the regulatory standard, nor are they reliable enough to undermine the robust animal toxicological data. *See* Sections V.A, V.B, *infra.* While EPA has considered certain *in vitro* studies in the past regarding purported neurodevelopmental effects below the current regulatory standard, these *in vitro* studies have not been validated in *in vivo* studies (*i.e.*, studies conducted in a living organism such as a laboratory animal) and are not based on conditions of real-world human exposure, and thus lack meaningful relevance to human risk assessment. EPA itself has recognized that *in vitro* studies must be considered with great caution, and in the absence of appropriate validation that *in vitro* methodologies and/or findings are relevant to *in vivo* outcomes, *in vitro* findings alone are not sufficient to infer potential human health risks.

As discussed in Section VI, *infra,* the Columbia, CHAMACOS, and Mt. Sinai epidemiology studies that have been cited as showing a link between chlorpyrifos exposure and neurodevelopmental effects have shown only questionable and inconsistent statistical associations, not causation. The Columbia study, in particular, has served as the centerpiece of Petitioners' claim that neurodevelopmental effects are associated with exposures below the current regulatory standard. But EPA's own SAP has cited weaknesses in the Columbia and other epidemiology studies, questioned their scientific validity and reliability on several occasions, and—as recently as 2016—rejected the use of these studies to support a proposed new regulatory endpoint. Numerous commenters, including the U.S. Department of Agriculture, have consistently criticized the reliability of the Columbia study for use in regulatory decision-making. *In addition, a very recent analysis of Columbia study data by Toxicology Excellence for Risk Assessment ("TERA") raised a number of additional, significant concerns about the reliability of the Columbia study's conclusions. See* Appendix B. The bottom line, as discussed herein, is that the Columbia study relies on spot samples of questionable analytic merit, and has served as the very weak underpinning for every related publication that has followed.

Moreover, the neurodevelopmental outcomes in the epidemiology studies advanced by Petitioners have been over-generalized across studies. The specific results are not replicated in other studies, undermining the claim of a link between neurodevelopment effects and chlorpyrifos exposures. In fact, consideration of the findings *in total across* these studies, does not support and even counters such a claim. Indeed, as time has passed, more epidemiology studies have been conducted studying chlorpyrifos. The results of these studies show no consistent, clear evidence of any associations between prenatal or childhood exposure to chlorpyrifos at levels below the current regulatory standard and adverse neurodevelopmental effects, further undermining the reliability of the Columbia, CHAMACOS, and Mt. Sinai studies.

Also, many factors can influence childhood development—both for better or worse—and could also be correlated with the effects reported. Most of these factors were unmeasured in the epidemiology studies, but are important in understanding the underlying factors of childhood development. These alternate explanations need to be fully considered and accounted for when attempting to establish any causation.

Moreover, as discussed *infra* in Section V.C, no reliable, science-based alternative mode of action associated with putative neurodevelopmental/behavioral effects has been identified at exposure levels below those that would trigger cholinesterase inhibition. And, as EPA's SAP stated in 2016, "there does not appear to be biological plausibility" for effects from chlorpyrifos exposures that are below the level that would trigger cholinesterase inhibition. 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 41 (July 20, 2016).

As further discussed *infra*, Section VII.A, the FQPA and the FFDCA are guided by two fundamental threshold principles: first, they are not statutes based on the precautionary principle, under which all doubt must be exhausted before a crop protection product may be registered. Rather, the food safety standard under the FFDCA and the FQPA is based on reasonable certainty of no harm. Second, the Agency must have valid, reliable data in order to make regulatory decisions, including to set a safety factor. Here, there are no valid, reliable data to call into question the current regulatory standard for chlorpyrifos.

As discussed *infra* in Section VIII.A, Petitioners and the States' Objections are replete with misstatements and false assertions. The Objections misrepresent the scientific and

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regulatory history for chlorpyrifos. Petitioners represent that the lack of safety for chlorpyrifos is uncontroverted when, in fact, substantial valid and reliable science exists to support the safety of this product under FQPA's reasonable certainty of no harm standard. Petitioners assert that the Agency has made conclusive scientific findings that chlorpyrifos is unsafe at the current regulatory standard, but fail to acknowledge that EPA has not changed its 2006 final determination that chlorpyrifos is safe at the current regulatory standard. As further discussed *infra,* Section VIII.A, all of EPA's subsequent statements about chlorpyrifos, made before the Agency considered a multitude of science-based comments, were simply part of the Agency's non-binding deliberative process. EPA's Order denying the Petition, made after the Agency's consideration of relevant science-based comments, expresses confidence that the current regulatory standard is protective of human health, consistent with recent findings in the European Union and Australia. Therefore, all claims that EPA found current potential exposures exceed acceptable risk from all possible sources, including food and water, are inaccurate.

While Petitioners suggest that chlorpyrifos poses a volatilization risk at the current regulatory standard, they present no new evidence in support. As more fully discussed *infra,* Section VIII.B, EPA's 2014 Revised Human Health Risk Assessment stated that "there is no anticipated risk[] of concern from exposure to the volatilization of either chlorpyrifos or chlorpyrifos oxon." Chlorpyrifos: Revised Human Health Risk Assessment for Registration Review ("2014 RHHRA") at 84 (Dec. 29, 2014).

Petitioners' Objections also rely on a declaration by Dr. Philip Landrigan. But, as discussed in Section VIII.D, that declaration is rife with errors and incorrect assumptions. In addition, Dr. Landrigan asserts that exposure to organophosphate pesticides has led to a loss of IQ points in children, citing an article by Dr. David Bellinger in support of this assertion. As discussed *infra,* Section VIII.D, Dr. Bellinger's article fails to undertake a systematic review of the epidemiology studies underlying its conclusions, and makes assumptions that are not scientifically justified. There is no credible evidence to suggest that chlorpyrifos exposure has led to a loss of IQ points in children.

Moreover, Petitioners' Objections wrongly assert that EPA has found unsafe drinking water contamination from chlorpyrifos. As discussed *infra,* Section VIII.E, and in DAS's prior comments, the Agency has not made any final determinations with respect to drinking water.

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EPA's drinking water assessment is still largely a screening-level assessment and not yet sufficiently refined or complete for purposes of human health risk assessment.

Finally, while Petitioners and the States assert that the Petition shifts the burden to the registrant or EPA to prove that chlorpyrifos is safe, neither the FFDCA nor the FQPA state that a petition to revoke already established tolerances shifts the burden of proving safety to the Agency or the registrant. In addition, the Objections cite no compelling authority for the argument that the Petition cannot be denied unless and until EPA affirmatively makes a new "safety" determination under the FFDCA.

III. REGULATORY HISTORY

In 2006, EPA completed its statutorily mandated reregistration of chlorpyrifos under FIFRA and the FFDCA. In a final decision that is still in effect, EPA reauthorized all existing agricultural uses for chlorpyrifos. EPA, Reregistration Eligibility Decision ("RED") for Chlorpyrifos (2006). In particular, pursuant to Section 408(b)(2) of the FFDCA, as amended by the FQPA, EPA determined that chlorpyrifos food tolerances (allowed pesticide residue limits) are "safe," meaning there is "a reasonable certainty that no harm will result from aggregate exposure to the pesticide chemical residue." 21 U.S.C. § 346a(b)(2)(A)(ii). Importantly, EPA's cumulative risk assessment in support of reregistration set an FQPA safety factor of 1X for the AChE inhibition endpoint for organophosphate pesticides ("OP"), including chlorpyrifos.

In 2007, PAN/NRDC filed the Petition with the Agency, seeking revocation of all chlorpyrifos tolerances and cancellation of all EPA registrations for products containing chlorpyrifos. The Petition was based, in significant part, on a taxpayer-funded epidemiology study conducted by researchers at Columbia University (the "Columbia study"), first published in 2002. The Columbia study claimed an association between *de minimis* amounts of chlorpyrifos allegedly found in the umbilical cord blood of a group of mothers almost twenty years ago with neurodevelopmental effects in their children later in life.

In response to the Petition, EPA accelerated the human health risk assessment process initiated as part of the Registration Review of chlorpyrifos. Under FIFRA, Registration Review is a periodic reassessment EPA is required to complete for all pesticide registrations, 7 U.S.C. § 136a(g). During Registration Review, which is still ongoing, EPA conducted multiple risk assessments, which were released for comment but are not final Agency conclusions. EPA also

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convened several sessions of its FIFRA SAP, an independent advisory committee of scientific experts, *see* 7 U.S.C. § 136w(d)(1), to evaluate several scientific issues relating to chlorpyrifos, including the Columbia study. The SAP expressed significant concerns about the quantitative use of the Columbia study in risk assessment, among other issues. *See, e.g.*, 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 19 (July 11, 2012) ("[T]he Panel largely concurs with EPA that the data generated from [the epidemiology] studies alone are not adequate enough to obtain a point of departure (POD) for the purposes of quantitative risk assessment."); *see also* 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 ("2008 SAP Minutes") at 46 (Dec.17, 2008) ("The Panel agreed with the Agency that there were limitations in the [Columbia Study and two additional] epidemiological studies that precluded them from being used to directly derive the PoD or the uncertainty factor.").

In 2012, EPA issued a denial as to six of the ten claims raised in the Petition. EPA notified Petitioners that it would not issue a final denial as to those claims unless requested, and Petitioners made no such request. Instead, Petitioners sought mandamus relief in the U.S. Court of Appeals for the Ninth Circuit because they believed the process was taking too long. The Ninth Circuit denied Petitioners' original mandamus petition, finding no unreasonable delay by EPA. *In re Pesticide Action Network N. Am.*, 532 F. App'x 649, 651 (9th Cir. 2013). Petitioners then filed a new mandamus action with the Ninth Circuit in September 2014, asking the court to force EPA to make a decision on the Petition. *In re Pesticide Action Network N. Am.*, No. 14-72794 ("*PANNA II*") (9th Cir. Sept. 10, 2014).

From 2007 until 2015, EPA gave every indication that it intended to deny the Petition. As recently as March 2015, EPA informed both the Petitioners and the Ninth Circuit that it planned to deny the Petition, having determined, based on the results of its 2014 RHHRA, that the claims raised in the Petition did not provide a basis to revoke all chlorpyrifos tolerances and cancel all chlorpyrifos registrations. *See* Status Rep., *In re Pesticide Action Network N. Am.*, No. 14-72794, at 2 (9th Cir. Mar. 31, 2015), ECF No. 14. Specifically, EPA's March 26, 2015, letter to Petitioners advised Petitioners that it "does not believe the claims raised in your petition establish a basis to revoke all chlorpyrifos tolerances and cancel all chlorpyrifos registrations." *Id.*, Attach. 1 at 3. EPA explained, among other things, that the scientific evidence was

"insufficient" to depart from the 10% red blood cell acetylcholinesterase inhibition regulatory standard upon which EPA's 2006 safety determination was based. Id.

EPA then changed course, not due to any newfound concern related to the Petition, but based on purported drinking water exposure concerns the Agency was working to address that were raised from hypothetical modeling assessments. EPA advised the Ninth Circuit in the mandamus action in June 2015 that it intended to grant the Petition. *Id.*, Status Rep. at 1-2 (June 30, 2015), ECF No. 20. On August 10, 2015, the Ninth Circuit issued a mandamus order compelling EPA to "issue *either* a proposed or final revocation rule *or* a full and final response to the administrative petition by October 31, 2015." *Id.*, Op. at 12, ECF No. 23 (emphasis added).

On October 28, 2015, EPA issued a proposed rule to revoke all chlorpyrifos tolerances, this time based on the Columbia study and also on an initial, screening-level drinking water assessment, which EPA said it needed to further refine. Chlorpyrifos; Tolerance Revocations, 80 Fed. Reg. 69,080 (Nov. 6, 2015) (the "Proposed Rule"). EPA issued the Proposed Rule to comply with the Ninth Circuit's deadline, though it had not yet completed a full, refined drinking water assessment or had sufficient time to address a multitude of comments regarding the 2014 RHHRA, including the registrant's. As a result, EPA stated that it "may update this action with new or modified analyses as EPA completes additional work" and expressed its intent to allow the public to comment on that work prior to issuing a final rule. *Id.* at 69,083. Following issuance of the Proposed Rule, the Ninth Circuit extended the deadline for EPA to act on the Petition until December 30, 2016, and later extended the deadline until March 31, 2017. *In re Pesticide Action Network N. Am.*, No. 14-72794, ECF Nos. 29, 51.

Clearly not yet content with the scientific basis for its Proposed Rule, in April 2016, EPA convened the SAP to review a novel, unprecedented proposal developed by the Agency after issuance of the Proposed Rule that would base a new regulatory standard for chlorpyrifos directly on cord blood concentrations reported in the Columbia study. Echoing criticisms raised at SAP meetings, the 2016 SAP cited numerous deficiencies in the study and expressed concerns about reliance on the study in the absence of the underlying raw data, which Columbia researchers have steadfastly refused to provide, despite EPA's repeated requests—as recently as January 2018. *See* Chlorpyrifos: EPA's Seven Year Quest for Columbia's Raw Data, https://www.epa.gov/ingredients-used-pesticide-products/chlorpyrifos-epas-seven-year-quest-

columbias-raw-data. The SAP rejected EPA's proposal for a new regulatory standard, deeming the cord blood results from the study unreliable and insufficient for use in setting a point of departure. *See* 2016 SAP Minutes at 25 ("[T]he 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 [point of departure] for risk assessment as *premature and possibly inappropriate*.") (emphasis added).

Notwithstanding the SAP's admonition against using the Columbia study cord blood results for regulatory purposes, and still plainly not satisfied with the status of its scientific analysis, in November 2016, EPA proposed yet another, completely new regulatory standard that was also based principally on the Columbia study's conclusions, and thus the cord blood results the SAP rejected. *See* EPA, Chlorpyrifos: Revised Human Health Risk Assessment for Registration Review (Nov. 3, 2016) ("2016 RHHRA"). EPA did not convene the SAP to review this novel approach, which was severely criticized by public commenters, including the U.S. Department of Agriculture ("USDA") under the prior Administration, and other commenters. For example, in its comments on EPA's November 2016 proposal, USDA stated:

> [EPA's] latest risk assessment is still based on just the single, not replicated, and unconfirmed [Columbia] study. Many weaknesses inherent in the study have been identified by the SAP and others, which undermine its suitability for determining a point of departure. These weaknesses remain unaddressed in EPA's latest risk assessment. This cannot be the type of "sound, high quality science" the writers of EPA's Scientific Integrity Policy envisioned as the "backbone of the EPA's decision-making." USDA has grave concerns that ambiguous response data from a single, inconclusive study are being combined with a mere *guess* as to dose levels, and the result is being used to underpin a regulatory decision about a pesticide chemical that is vital to U.S. agriculture, and whose removal from the market would have a major economic impact on growers and consumers.

USDA Comments on the Risk Assessment Underlying the Reopened Proposed Rule "Chlorpyrifos; Tolerance Revocations; Notice of Data Availability and Request for Comment" (Docket ID EPA-HQ-OPP-2015-0653-0648), at 2 (Jan. 17, 2017).

On March 29, 2017, following a review of comments submitted on the Proposed Rule and 2016 RHHRA, EPA issued its Order denying the Petition. Chlorpyrifos; Order Denying PANNA and NRDC's Petition To Revoke Tolerances, 82 Fed. Reg. 16,581 (Apr. 5, 2017) (the "Order" or "EPA Order"). EPA acknowledged that it had "three times presented *approaches and*

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proposals" to the SAP for evaluating the epidemiologic evidence of chlorpyrifos exposure and neurodevelopmental effects. *Id.* at 16,590 (emphasis added). But, EPA stated:

> The SAP's reports have rendered numerous recommendations for additional study and sometimes conflicting advice for how EPA should consider (or not consider) the epidemiology data in conducting EPA's registration review human health risk assessment for chlorpyrifos. While industry and public interest groups on both sides of this issue can debate what the recommendations mean and which recommendations should be followed, one thing should be clear to all persons following this issue: *the science on this [issue] is not resolved* and would likely benefit from additional inquiry.

Id. (emphasis added).

In its March 29th Order, EPA stated that it had examined the evidence cited by Petitioners and concluded that it failed to show that chlorpyrifos is not safe. *Id.* at 16,587, 16,588. EPA also stated in its Order that animal toxicology data "support the FQPA safety factor of 1X for the AChE inhibition endpoint used in the 2006" cumulative risk assessment for organophosphate pesticides, including chlorpyrifos. *Id.* at 16,589. EPA expressed confidence in AChE inhibition as the appropriate regulatory endpoint. *Id.* With respect to epidemiology studies claiming an association between chlorpyrifos exposure at levels below the current regulatory standard and neurodevelopmental effects, EPA said that the studies were inconclusive and required further scientific review. *Id.* Thus, EPA denied the remaining Petition claims and issued a full and final denial of the Petition. *See id.* at 16,583 ("In this order EPA is denying the Petition in full.").

Importantly, in its Order, EPA stated that its decision "[f]ollow[ed] a review of comments on both the November 2015 [Proposed Rule] and the November 2016 [RHHRA]." *Id.* This is the first time EPA indicated that it had reviewed comments from interested stakeholders like growers, grower groups, the primary registrants, and USDA addressing the possible revocation of tolerances for chlorpyrifos.[3]

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[3] For ease of reference, DAS's prior comments are as follows, and are incorporated by reference: (1) Dow AgroSciences LLC's Response to EPA's Revised Human Health Risk Assessment for Chlorpyrifos Registration Review dated April 29, 2015, EPA-HQ-OPP-2015-0653-0214 (hereafter referred to as "DAS Response to RHHRA"); (2) 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 (including all references and appendices therein) (hereafter referred to as

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Soon after the Order was issued, PAN/NRDC filed a motion with the Ninth Circuit for "further mandamus relief," challenging the Administrator's alleged failure to make "new safety findings" supporting his denial of the administrative petition. *PANNA II*, at 3, ECF No. 55. The Ninth Circuit denied the motion on the ground that EPA had complied with the Court's orders by issuing a "final response to the petition." *Id.* at 4, ECF No. 65. The Ninth Circuit instructed PAN/NRDC that the administrative objections process under the FFDCA was the pathway to obtaining judicial review. *Id.* (citing 21 U.S.C. §§ 346a(g)(2), (h)(1); 40 C.F.R. §§ 178.65, 180.30(b)).

On June 5, 2017, Petitioners and the States filed objections, challenging the EPA Order on what they allege are purely legal grounds. In particular, Petitioners and the States assert that there is "overwhelming" scientific evidence that chlorpyrifos is unsafe at the current regulatory

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"DAS Response to Proposed Rule"); (3) Burns, C. 2015, Comments on EPA's Literature Review on Neurodevelopment Effects & FQPA Safety Factor Determination for the Organophosphate Pesticides, dated December 22, 2015 (document posted in docket EPA-HQ-OPP-2010-0119), submitted by G. Oliver, Dow AgroSciences LLC, EPA-HQ-OPP-2015-0653-0230 (hereafter referred to as "DAS Comments Regarding Epidemiology"); (4) DAS (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 (hereafter referred to as "DAS Legal Comments Regarding Proposed Rule to Revoke Tolerances for Chlorpyrifos"); (5) Dow AgroSciences LLC's Response to EPA's Chlorpyrifos-Methyl: Human Health Draft Risk Assessment (DRA) for Registration Review, dated September 15, 2015, EPA-HQ-OPP-2010-0119-0044 (hereafter referred to as "DAS Response to EPA's Draft Risk Assessment for Chlorpyrifos-Methyl"); (6) DAS Legal and Policy Comments in Response to (i) EPA's Literature Review on Neurodevelopment Effects & FQPA Safety Factor Determination for 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 (hereafter "DAS Literature Review Comments"); (7) Dow AgroSciences LLC's Comments on 2016 Notice of Data Availability, Revised Human Health Risk Assessment and Refined Drinking Water Assessment for Chlorpyrifos, dated January 17, 2017, EPA-HQ-OPP-2015-0653-0651 (hereafter "DAS Comments on 2016 RHHRA"); (8) C. Burns. 2017. Dow AgroSciences LLC Comments on EPA's Response to Comments for Public Comments Related to Applying the FQPA 10X Safety Factor for the Organophosphate Pesticides (document dated December 29, 2016, EPA-HQ-OPP-2008-0316-0071). Submitted by G. Oliver to docket EPA-HQ-OPP-2010-0119; and (9) DAS (Dow AgroSciences). 2017. DAS Legal and Policy Comments in Response to (i) Response to Comments for Public Comments Related to Applying the FQPA 10X Safety Factor for the Organophosphate Pesticides; (ii) Organophosphates: Response to Occupational and Residential Exposure-Related Comments on the Preliminary Organophosphate Human Health Risk Assessments; and (iii) Response to Dietary-Related Comments on the Preliminary Organophosphate Human Health Risk Assessments. Dated July 24, 2017 (EPA docket: EPA-HQ-OPP-2010-0119).

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standard, that EPA had previously made a finding that chlorpyrifos was unsafe, and that the burden was on EPA to make a new safety determination when denying the administrative petition to revoke tolerances. As outlined further in this Response, DAS disagrees with all of these assertions on a factual, scientific, and legal basis.

DAS submits this Response to Objections to correct the many false and inaccurate representations about chlorpyrifos and its regulatory history that are set forth in the Objections. Moreover, as set forth herein, and in the multitude of comments to the docket from DAS and other stakeholders, a robust set of reliable toxicology data support EPA's current regulatory standard for chlorpyrifos. Epidemiology and other studies that the Objections assert demonstrate otherwise are unreliable and invalid for purposes of regulatory decision-making, and must not be relied on to take such a draconian and significant regulatory action like a tolerance revocation.

IV. CHLORPYRIFOS IS CRITICAL TO GROWERS.

A. Chlorpyrifos Is an Essential Agricultural Crop Protection Tool.

Chlorpyrifos is an organophosphorus insecticide first registered in the United States in 1965. Chlorpyrifos currently protects 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. In situations of a sudden outbreak of a new pest, growers often go to chlorpyrifos as a proven tool for control and to prevent widespread yield loss.

Chlorpyrifos exhibits moderate mammalian toxicity (WHO Hazard Class II) and is not carcinogenic, a selective reproductive or developmental toxicant, or an endocrine disruptor. EPA has used inhibition of blood cholinesterase as a protective regulatory health endpoint, PoD, for risk assessment for over forty-five years.

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

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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.

A study of the benefits of chlorpyrifos to U.S. growers was submitted to the chlorpyrifos tolerance revocations docket in 2016 (Nelson, J.E., Schneider, L.L. *Use and Benefits of Chlorpyrifos in Agriculture*. Submitted to docket EPA-HQ-2015-0653 (January 2016)). 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 docket. In addition, multiple grower groups and many individual growers have provided comments throughout the various EPA public comment periods expressing the need for chlorpyrifos.

B. Loss of Chlorpyrifos Uses Would Have Significant Negative Impacts on Trade.

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. Revocation of U.S. tolerances would create a significant regulatory gap for U.S. food import standards and result in a state of regulatory disharmonization between the United States and the other 165 member countries of Codex. Indeed, EPA has never fully assessed the potential impact of the loss of use of chlorpyrifos.

Revoking chlorpyrifos tolerances would also significantly disrupt the pest management practices used in the production of certain import crops, impair long-standing trade relationships, and create a new set of winners and losers as market participants adapt to regulatory changes. Revocation of tolerances would have a significant impact on trade particularly with regard to developing countries that rely on exports of agricultural commodities to the United States. Nelson, J.E., Schneider, L.L. *The Impact of Revoking Chlorpyrifos Tolerances (MRLs) on U.S. Agricultural Imports from Key Food Exporting Countries*. Docket: EPA-HQ-OPP-2015-0653-0526 (Jan. 2017). Numerous foreign trade and government groups also commented on the need for these tolerances during the various EPA public comment periods.

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Nelson and Schneider assessed 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. They reported that revoking chlorpyrifos tolerances would potentially have a significant economic impact on consumers and food chain members in the United States, as well as on the exporting countries:

> 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.

Id. at 4–5.

V. SCIENTIFIC FRAMEWORK: The Current Regulatory Standard for Chlorpyrifos is Based on Decades of Solid Science.

A. EPA Has a Robust and Complete Set of Animal Toxicology Data that Supports its Current Safety Determination; Recent Experimental Toxicology Studies Reviewed by EPA and the California DPR Do Not Support Any Changes to that Standard.

As discussed in DAS's prior comments, over fifty years of robust animal toxicology data conducted during the registration and reregistration review process for chlorpyrifos show that chlorpyrifos meets the EPA standard for safety. *See* Declaration of Dr. Jennifer Seed ("Seed Decl."), Attach. A, ¶ 12 ("For many years, a complete and reliable animal toxicology data set, including reliable developmental neurotoxicity data, have supported the current regulatory standard for chlorpyrifos."). Further, "the animal toxicology data set for chlorpyrifos is complete and reliable and demonstrates (i) a well-established mode of action (AChE inhibition) and (ii) that there is no hazard identified to date that EPA has not accounted for under the current regulatory standard with respect to children's susceptibility." *Id.* ¶ 13.

EPA confirmed the reliability of the toxicological database for chlorpyrifos in its 2011 Preliminary Human Health Risk Assessment for chlorpyrifos, in which it stated that "[t]he toxicological database for chlorpyrifos is extensive and is adequate to support the registration review." PHHRA at 22. The Agency observed that "[t]he toxicity database includes the standard battery of guideline studies as well as special studies conducted by the registrant." *Id.* at 36. The Agency also stated that the available data showed "that cholinesterase inhibition

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(ChEI) provides the most sensitive dose-response information for deriving points of departure for chlorpyrifos." *Id.* at 7. The Agency went on to describe the extensive scope of animal studies supporting chlorpyrifos:

> [the] studies consider different durations of exposure (acute, short-, intermediate-term and chronic) and relevant routes of exposure (oral, dermal, and inhalation), different laboratory animal species, reproductive and developmental toxicity, neurotoxicity, developmental neurotoxicity (DNT), new acute and repeat dose comparative cholinesterase assays (CCA) for both chlorpyrifos and chlorpyrifos oxon, a special acute inhalation toxicity study and a required immunotoxicity study.

Id. at 36.

Use of this endpoint was also confirmed as recently as 2014 by the EFSA and the APVMA, and also remains the gold standard and point of departure used by the World Health Organization and virtually all major global regulatory authorities. *See, e.g.,* APVMA, Reconsideration of Chlorpyrifos at 1 ("[C]holinesterase inhibition remains the most sensitive and relevant adverse effect caused by chlorpyrifos and is therefore the most appropriate endpoint for the establishment of health based guidance values used to protect the entire population including pregnant women, infants and children."); EFSA Scientific Panel on Plant Protection Products and their Residues, Minutes of the 70th Plenary Meeting Held on 08-09 October 2014, Parma (Italy) ("PPR Panel Minutes") at 9 ("Considering the available studies, cholinesterase inhibition was considered the most sensitive endpoint on which reference values should be based."); World Health Organization, Chlorpyrifos in Drinking-Water, Background document for development of WHO Guidelines for Drinking-water Quality at 3 (2004) ("In long-term studies, inhibition of cholinesterase activity was again the main toxicological finding in all species.").

The 2014 RHHRA also confirmed that AChE inhibition is an appropriate regulatory endpoint: "AChE inhibition remains the most robust quantitative dose response data and thus continues to be the critical effect for the quantitative risk assessment." 2014 RHHRA at 24. The Agency also described the strength of the animal toxicological data:

> There are many chlorpyrifos studies evaluating AChE inhibition in red blood cell (RBC) or brain in multiple lifestages (gestational, fetal, post-natal, and non-pregnant adult), multiple species (rat, mouse, rabbit, dog, human), methods of oral administration (oral gavage with corn oil, dietary, gavage via milk) and routes of exposure (oral, dermal, inhalation via vapor and via aerosol). In addition, chlorpyrifos is unique in the availability of ChE data from peripheral tissues in some studies (e.g., heart, lung, liver). There are also literature studies comparing the *in vitro* ChE response to a variety of tissues (Chambers, 2013) which show

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> similar sensitivity and intrinsic activity. Across the database, brain AChE tends to be less sensitive than RBC AChE or peripheral ChE. In oral studies, RBC AChE inhibition is generally similar in response to peripheral tissues. *Thus, the in vitro data and oral studies combined supports the continued use of RBC AChE inhibition as the critical effect for quantitative dose-response assessment.*

Id. (emphasis added).

Petitioners claim that a growing body of animal toxicology data supports epidemiology studies claiming associations between chlorpyrifos exposure at levels below the current regulatory standard and neurodevelopmental effects. DAS has detailed the flaws and limitations in these animal studies in prior comments to EPA[4]; it is indefensible for EPA to use these studies as a basis for the significant regulatory action requested by Petitioners. As further summarized in the attached Appendix A, other animal toxicology studies more recently considered by EPA and the California Department of Pesticide Regulation are not viable or reliable for use in science-based decision-making due to deficiencies and limitations in their study design—including, in many studies, use of a single dose, use of doses that exceed those known to cause cholinesterase inhibition, use of subcutaneous injection as the route of exposure, use of dimethyl sulfoxide ("DMSO") as a vehicle, and/or failure to measure cholinesterase inhibition.

B. *In Vitro* Studies Do Not Create Uncertainty With Respect to the Current Regulatory Standard for Chlorpyrifos.

"EPA has long relied on *in vivo* 'apical' endpoints as the primary bases for the regulation of chemicals. These apical endpoints are empirically identified outcomes in intact animals exposed to the chemical at issue." Declaration by Dr. James Bus ("Bus Decl."), Attach. B, ¶ 11. In contrast, *in vitro* study outcomes are typically not regarded as apical endpoints because *in vitro* studies look at effects on only a group of cells or isolated organs in a test tube. *Id.* "Effects observed only in cells or isolated organs in a test tube do not reflect the overall complex biological functions of the intact organism that ultimately determine the end toxicological effect, and do not account for the full range of homeostatic and protective mechanisms that occur in an

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[4] *See, e.g.,* Dow AgroSciences LLC's Response to EPA's [RHHRA] for Chlorpyrifos Registration Review, EPA Dkt. EPA-HQ-OPP-2008-0850-0845, at 57–64 (Apr. 2015); Dow AgroSciences LLC's Comments on 2016 [NODA/RHHRA] and Refined Drinking Water Assessment for Chlorpyrifos, EPA Dkt. EPA-HQ-OPP-2015-0653-0651, at 33 and Appendix D (Jan. 2017); *see also* Dow AgroSciences LLC's Amicus Brief in Support of EPA, *League of United Latin Am. Citizens, et al. v. Wheeler*, No. 17-71636, ECF No. 72-2, at 20–23 (9th Cir. Mar. 15, 2018).

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in vivo animal." *Id.* "While the Agency may consider both *in vitro* and *in vivo* studies in its risk assessments, *in vitro* studies present numerous challenges that make them much less reliable for human health assessments than *in vivo* studies." *Id.* ¶ 10.

In the past, EPA has referred to *in vitro* studies of chlorpyrifos by Howard *et al.* (2005), Schuh *et al.* (2002), and Yang *et al.* (2008) and "suggested that these studies . . . create some additional 'uncertainty' concern regarding conclusions from high quality *in vivo* studies that indicate developmental neurotoxicity is observed only under conditions sufficient to cause maternal and fetal/pup AChE inhibition. [However, such] an additional uncertainty concern is not warranted by an examination of the whole animal, developmental neurotoxicity data." *Id.* ¶ 18. A review of the *in vitro* studies shows that "[t]here is no scientific basis for the Agency to infer uncertainty from *in vitro* data reporting neuronal cell effects at sub-AChE-inhibiting test concentrations [because] those effects have not been affirmed in a robust set of animal toxicological data supporting the current regulatory standard (*e.g.*, Maurissen *et al.*, 2000, Mattsson *et al.*, 2000)." *Id.* ¶ 20.

Further, "[f]or *in vitro* studies to be relevant for risk assessment, the test concentrations in the test tube or laboratory dish must have interpretable and meaningful relevance to human exposures." *Id.* ¶ 10. "Frequently, concentrations at which positive responses are observed *in vitro* are far removed from real-world human exposure conditions, thus rendering reliance on these *in vitro* studies inappropriate for risk assessment." *Id.* Thus, if it cannot be proven that the *in vitro* endpoints are relevant to apical *in vivo* outcomes, *in vitro* findings alone are not sufficient as a basis for assessment of potential human health risks. *Id.* ¶ 12. EPA has recognized that *in vitro* studies must be considered with great caution. *Id.* ¶ 14 (citing *EPA, Human Exposure Estimates and Oral Equivalents of In Vitro Bioactivity for Prioritizing, Monitoring and Testing of Environmental Chemicals* (2010)).

EPA has clearly delineated its expectation that *in vitro* findings be relevant to apical *in vivo* outcomes in its "Endocrine Disruptor Screening Program (EDSP) guidance[,] in which a two-tiered testing approach has been implemented (EPA, 2009)." *Id.* This Program "requires that the mostly *in vitro* tier 1 screening-level tests be validated against apical *in vivo* responses. In other words, the EDSP requires that positive findings in *in vitro* tier 1 must be directly correlated with adverse outcomes in *in vivo* apical tier 2 tests *before* such *in vitro* tests can be used as screening-level indicators of potential toxicological hazards." *Id.* ¶ 12 (emphasis added).

"Thus, relying on *in vitro* studies conducted at the test tube or lab dish scale alone are not sufficient to supplant a failure to identify corresponding apical responses in more robust and high-quality *in vivo* studies. To do otherwise would undermine EPA's long-held reliance on whole animal studies to determine apical endpoints and the dose-response thereof as most appropriate for the purpose of risk assessment." *Id.*

Moreover, numerous conditions used in the *in vitro* studies considered by EPA and others call into question reliance on these experimental data for regulatory decision-making. For example, Howard (2005) and Yang (2008) used DMSO as a carrier solvent for the chlorpyrifos or chlorpyrifos oxon test material. The concentration of DMSO could have a substantial impact on many of the measured results. Cavaletti *et al.* have shown that intraperitoneal administration of dilute solutions of DMSO can have a significant impact on the nervous system. Cavaletti *et al.* (2000), *Effect on the Peripheral Nervous System of Systemically Administered Dimethylsulfoxide in the Rat: a Neurophysiological and Pathological Study*. Toxicol. Ltrs. 118: 103-07. They caution researchers that "[t]he neurophysiological and pathological changes observed in our study are severe enough to merit careful consideration in the course of experimental studies involving DMSO as a solvent for drugs which are under evaluation for their potential neurotoxicity." *Id.* at 103. Other authors have shown that DMSO used as a dose vehicle can also enhance the clinical symptoms of organophosphates. Ballough *et al.* (2008), *Brain Damage from Soman-Induced Seizures is Greatly Exacerbated by Dimethyl Sulfoxide (DMSO): Modest Neuroprotection by 2-aminoethyl diphenylborinate (2-APB), a Transient Receptor Potential Channel Inhibitor and Inositol 1,4,5-triphosphate Receptor Antagonist*, J. Med. CBR Def 6: 1-20; Carr *et al.* (2008), *Effect of Different Administration Paradigms on Cholinesterase Inhibition Following Repeated Chlorpyrifos Exposure in Late Preweanling Rats*. Toxicol. Sci. 106: 186-92. Further, "[a]lthough the Howard *et al.* (2005) and Yang *et al.* (2008) studies diluted the 100% DMSO stock solutions by 1:1000 for final cell culture, this dilution approximates the DMSO dose (1 ml/kg = 1 ml/1000 ml) that is neurotoxic *in vivo*." Bus Decl. ¶ 22.

The 2012 SAP echoed these concerns about the use of DMSO: "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." 2012 SAP Minutes

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at 12. The Agency recognized in its charge question to the 2012 SAP that it should exercise caution in making connections between possible effects observed in the above-referenced *in vitro* studies and effects *in vivo*: "Some of these comparisons must be considered with caution since the amount of change in the *in vitro* systems required to elicit an adverse effect *in vivo* is unknown. Moreover, extrapolation from *in vitro* perturbations to *in vivo* effects has not been established. . . ." 2012 SAP Minutes at 13. The SAP agreed with the Agency's concerns:

> The Panel concurs with the Agency that caution should be applied in interpreting the *in-vivo* significance of the changes observed across the various *in vitro* studies. Several uncertainties and limitations are associated with the translation of *in vitro* study results to *in vivo* effects. The inherent complexity of the nervous system presents significant challenges to accomplishing this translation. An additional example of uncertainty is that cells that are isolated in culture within an *in vitro* experiment may be affected differently than they would if they were within their *in vivo* environment.

Id. at 14.

At least one court has also noted the limitations of relying on *in vitro* studies. In *In re Ephedra Prods. Liab. Litig.*, 393 F. Supp. 2d 181, 194 (S.D.N.Y. 2005), the court observed that "the gaps between [*in vitro*] data and definitive evidence of causality are real and subject to challenge before the jury[.]"). Other scientists have echoed these concerns: the "weakness of [*in vitro*] studies is the uncertainty that the effects observed at cell level would occur in the 'real world' of the complex living organism." Huber *et al.* (2011), *Organic Food and Impact on Human Health: Assessing the Status Quo and Prospects of Research*, Wageningen J. of Life Sci. 58: 103-09, at 105.

In sum, the *in vitro* studies cited by EPA and others in the past do not create uncertainty with respect to the current regulatory standard for chlorpyrifos.

C. There Is No Reliable Science to Support a Mode of Action Other Than Cholinesterase Inhibition.

Over the last several years, significant attention has focused on whether non-cholinergic modes of action exist for chlorpyrifos and, if they do, whether they may be operating at dose levels below which cholinesterase inhibition occurs. But no such non-cholinergic mode(s) of action has been observed in the significant number of Guideline studies (covering many endpoints that would detect impacts on development or neurodevelopment) that have been conducted over more than forty years as part of EPA's registration and reregistration processes for chlorpyrifos.

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Many of the studies that have purportedly shown non-cholinergic effects associated with neurodevelopmental effects were not designed for regulatory decision-making or risk assessment purposes. In addition, specific hypotheses evaluating potential non-cholinergic mode(s) of action have not been adequately proposed, tested, or validated in appropriate animal models. Both EPA and its SAP have concluded, upon review of the scientific literature, that there are insufficient data to support a potential non-cholinergic mode(s) of action for chlorpyrifos. For example, when asked about a possible non-cholinergic mode of action for chlorpyrifos, the 2008 FIFRA SAP stated that

> [t]here was a consensus of the Panel that available data were inadequate to support a weight of evidence evaluation for non-cholinergic mode(s) of action for the behavioral alterations following gestational and early postnatal exposure to chlorpyrifos that persisted into adulthood. The Panel agreed that the available information does not allow for behavioral endpoints to be considered as a point of departure and recommended, based upon currently available data, that cholinesterase inhibition be used as the PoD.

2008 SAP Minutes at 28. *See also id.* at 56 ("[T]here is a clear lack of identifiable key events for mode of actions not related to AChE inhibition.").

D. Reliance on Prior EPA Dose Reconstruction for Exposure Assessment Does Not Lead to Reliable Results.

In its 2014 RHHRA, the Agency suggested that it could make up for the lack of raw data underlying the Columbia study by conducting a dose reconstruction, which "showed that using high end exposure assumptions . . . peak RBC AChE inhibition was predicted to be only 0.45%" (thus supporting a 10X safety factor). EPA, Response to Comments for Public Comments Related to Applying the FQPA 10X Safety Factor for the Organophosphate Pesticides at 19, published May 25, 2017 in docket: EPA-HQ-OPP-2010-0119-0055 ("Response to Comments").

The dose reconstruction was based in large part on hearsay and questionnaires that did not assess which particular pesticide study participants had been exposed to. The results of the dose reconstruction are therefore unreliable—"[a] tenuous, opaque dose reconstruction based on questionnaires presented to study participants, which EPA recognized as having limitations and which did not undergo peer review, cannot support the conclusion that using high end exposure assumptions results in peak RBC AChE inhibition of only 0.45%. The dose reconstruction simply does not provide data that are reliable or valid." Declaration of Dr. Jeffrey Driver ("Driver Decl."), Attach. C, ¶ 21.

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In its 2016 RHHRA, EPA reviewed the registered home uses that would have been available to the Columbia study cohort to develop a new PoD for risk assessment from internal concentrations of chlorpyrifos. 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. However, "there is no definitive evidence that chlorpyrifos was applied by indoor crack and crevice application methods in any of the residences of the Columbia cohort, and many study subjects changed residences frequently during the study." *Id.* ¶ 22. Therefore, crack and crevice dose reconstruction "should not be used to establish a route-specific PoD, especially given the deficiencies associated with the Columbia cohort data." *Id.* ¶ 23.

Further, the underlying premise that the effects purportedly observed and claimed to be linked to chlorpyrifos exposures from these crack and crevice treatments is unfounded since "there were members of the cohort that received crack and crevice applications without the claimed health effects, and the entire cohort could have had exposures through diet and water, which would be higher than through the added crack and crevice exposure." *Id.* ¶ 23. *See also* DAS Comments on 2016 RHHRA at 35-41; Driver *et al.*, Public Comments: Chlorpyrifos Revised Human Health Risk Assessment for Registration Review (EPA's Office of Pesticide Programs, November 3, 2016) (EPA-HQ-OPP-2015-0653-0647) (Jan. 16, 2017).

VI. EPIDEMIOLOGICAL STUDIES ARE NOT RELIABLE ENOUGH FOR REGULATORY DECISION-MAKING AND SHOULD NOT IMPACT THE CURRENT REGULATORY STANDARD.

Petitioners urge that the Columbia, Mt. Sinai, and CHAMACOS studies show that chlorpyrifos is not safe at the current regulatory standard. But the conclusions in the Columbia study are based on unreliable blood test results (as well as multiple additional deficiencies), and a new analysis of some data from a Columbia study publication raises additional significant questions about the scientific validity of the study's conclusions. Moreover, the Mt. Sinai, CHAMACOS, and other epidemiology studies are inconsistent and do not support the published conclusions in the Columbia study.

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A. The Cord Blood Measurements in the Columbia Study Are Not Valid or Reliable, and Any Published Conclusions Drawn from Those Measurements are Therefore Not Valid or Reliable for Regulatory Decision-Making.

i. The 2008 and 2016 SAP Heavily Criticized the Validity and Reliability of the Columbia Study's Cord Blood Measurements.

The 2008 and 2016 SAP raised numerous doubts about the reliability and validity of the cord blood data that form the basis of the conclusions drawn in the study, both as to the reliability and accuracy of the analytical methodology used to derive results, and as to whether the results represent an accurate picture of exposure. *See, e.g.,* Transcript of April 2016 SAP Meeting ("2016 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."); *id.* at 768 ("[T]here are a lot of uncertainties in the data . . . I don't think the data are very strong."). The 2016 SAP expressed concerns with, among other issues, the Columbia researchers' arbitrary assignment of values for over 40% of the children in the Columbia study who had chlorpyrifos levels that were below the level of detection[5] and use of a surrogate measurement for 12% of children for whom they lacked any chlorpyrifos measurements at all; the use of a single point in time measurement to estimate exposure; and the lack of biological plausibility for how the extremely low levels of chlorpyrifos reported in the study could produce the effects claimed. These levels in the pg/g range are several-fold lower than the current regulatory endpoint. Specifically, the 2016 SAP said that:

- "A major source of uncertainty for the Panel was the lack of verification and replication of the analytical chemistry results that reported very low levels of chlorpyrifos (pg/g). Imputing quantitative values when the concentration of analyte falls below the level of detection (LOD) was a particular concern, especially given that a large fraction of cord blood samples included in the analyses presented with levels below LOD." 2016 SAP Minutes at 18; *see also id.* at 41 ("[T]he use of means with large standard deviations that extend below the level of detection that are included in the analysis . . . further decreases the value and increases uncertainties associated with the raw data that cannot and has not been independently reviewed or verified.").

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[5] *See* Rauh *et al.*, *Seven-Year Neurodevelopmental Scores and Prenatal Exposure to Chlorpyrifos, a Common Agricultural Pesticide*, 119 Environ Health Persp 1196, 1198 (2011) (stating that cord blood measurements for 43% of the Columbia cohort fell below the limit of detection).

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- "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 22–23.
- "The assumption that the impaired working memory and lower IQ measures observed are caused primarily by a single insecticide (chlorpyrifos) and predicted by the blood levels at time of delivery is not supported by the scientific weight of evidence." *Id.* at 23.
- "Some Panel members stated that the reliance on single cord blood measurements from only one study (i.e., the CCCEH study) as a primary basis for a highly impactful regulatory decision goes against standard practices of science in the fields of toxicology and pharmacology." *Id.* at 42.
- Noting the majority view that there is a "lack of biological plausibility for how low cord blood (low parts per trillion) concentrations of chlorpyrifos can alter working memory and produce neurodevelopmental impairment." *Id.* at 25-26.
- "And a single study, single point in time, questionable, extremely low values, no biological plausibility – there's nothing I'm aware of in the literature that would suggest[,] you know, [picomolar] levels cause some significant neuronal change that could underlie a prefrontal cortex-based memory task." 2016 SAP Tr. at 628.
- "Well if [the chlorpyrifos measurements in the cord blood samples are] below the level of detection for that study then that, in my mind raises an issue with the validity of that study." *Id.* at 663.

As one Panel member aptly stated, the Columbia Study "is plagued by issues that diminish the enthusiasm for this study." *Id.* at 622.

Moreover, the 2016 SAP made several statements that undermine any contention that there are purported effects at exposures below the current regulatory standard. For example, the 2016 SAP Minutes state that "*[W]ithout 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). The 2016 SAP also pointed out that effects at these extremely low levels are rarely seen even with the most potent acetylcholinesterase-inhibiting drugs:

> 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 (IC_{50}'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 IC_{50} 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.

Id. at 54.

The 2008 SAP also expressed similar concerns about the cord blood measurements. *See, e.g.,* 2008 SAP Minutes at 34 ("[T]he single measurement of cord blood chlorpyrifos may not be representative of the total exposure during pregnancy, but only reflects exposure [that] happened in the few days before delivery."); *id.* at 45 ("One of the key limitations of the epidemiological studies is that the exposure data were collected at single time point and lack information on the long-term exposure level and duration.").

In sum, the 2008 and 2016 SAP identified a number of deficiencies and limitations in the Columbia study, including as to the validity and reliability of the reported test results. These deficiencies and limitations have been further discussed in detail in DAS's prior comments. *See, e.g.,* DAS Comments on 2016 RHHRA § IV and App'x B; DAS Comments on 2014 Revised Human Health Risk Assessment § 4.2.2; Dow AgroSciences Additional Comments for the EPA's FIFRA Scientific Advisory Panel (SAP): Chlorpyrifos: Analysis of Biomonitoring Data (April 19–21) (April 15, 2016), Docket EPA-HQ-OPP-2016-0062).

Moreover, EPA's 2016 Updated Literature Review of epidemiology studies recognizes numerous deficiencies in the Columbia study. *See* EPA, Updated Literature Review on Neurodevelopment Effects & FQPA Safety Factor Determination for the Organophosphate Pesticides, published May 25, 2017 in docket: EPA-HQ-OPP-2010-0119-0060 ("Updated Literature Review") at 49–62. For example, the Updated Literature Review states that a weakness of the Columbia study is the fact that "[t]he use of a single snapshot of prenatal chlorpyrifos exposure may not be an accurate surrogate for full prenatal exposure levels." *Id.* at 59; *see also id.* at 54 (criticizing "[r]eliance on a single exposure level (prenatal/cord blood.)"). *See also* Declaration by Dr. Carol Burns ("Burns Decl."), Attach. D, ¶ 13 ("It is fundamentally flawed to use a single biological sample of a short-lived chemical to infer the level of past exposure. . . . Researchers have cautioned against relying upon a single sample to estimate long

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term exposure (Morgan *et al.* 2016, LaKind and Naiman 2015, Spaan *et al.* 2015, Aylward *et al.* 2014). Exposure assessments based upon a 'single sample without considering error' are considered to be of low utility (LaKind *et al.* 2014)."); *id.* ¶ 11 ("[T]he Columbia and Mt. Sinai studies relied upon a single biological sample collected at delivery. Due to the short half-life of chlorpyrifos in the body, the concentration of chlorpyrifos or the metabolite are not a valid estimate of the exposure levels throughout the prenatal period."). The Updated Literature Review also observes that "[d]ue to the pervasive, non-specific nature of neurological effects, it is difficult to attribute causality." Updated Literature Review at 54–55. Finally, the Updated Literature Review states that one of the Columbia study publications "only included participants recruited in the post-cancellation period" and "the large number of observations below the level of detection receiving equal rank. . . may be problematic." *Id.* at 62.

A study with so many limitations and deficiencies is not only inappropriate as the basis for a point of departure, it should also not be used *for any purpose* in regulatory decision-making, including as support for setting an FQPA 10X safety factor or to suggest uncertainty with respect to the current regulatory standard. The Columbia study simply does not meet the statutory test for validity and reliability, by any measure.

ii. The Columbia Study's Conclusions Are Not Valid or Reliable Because they are Primarily Based on the Deficient Cord Blood Measurements.

Of critical importance, the Columbia study's conclusions are primarily based on cord blood measurements. Driver Decl. ¶ 17. Specifically:

- "[T]he conclusions set forth in the published articles for the Columbia study are predicated on a presumed dose-response related to cord blood level measurements of chlorpyrifos and neurodevelopmental outcome indicators." *Id.* ¶ 16.

- For example, the Columbia study investigators reported that "higher prenatal [chlorpyrifos] exposure, as measured in umbilical cord blood plasma, was associated with decreases in cognitive functioning on two different WISC-IV indices, in a sample of urban minority children at 7 years of age." Rauh *et al.* (2011), *Seven-Year Neurodevelopmental Scores and Prenatal Exposure to Chlorpyrifos, a Common Agricultural Pesticide,* 119 Environ Health Persp at 1200.

- "Using a different biomarker of exposure (the parent compound of [chlorpyrifos] in umbilical cord plasma), we have previously reported (in the same cohort as the present study) significant associations between prenatal exposure to [chlorpyrifos] (> 6.17 pg/g) and reduced birth weight and birth length (Whyatt *et al.* 2004), increased risk of small size for gestational age (Rauh V, Whyatt R, Perera F, unpublished data),

increased risk of mental and motor delay (< 80 points) and 3.5- to 6-point adjusted mean decrements on the 3-year Bayley Scales of Infant Development (Rauh *et al.* 2006), and evidence of increased problems related to attention, attention deficit hyperactivity disorder, and pervasive developmental disorder as measured by the Child Behavior Checklist at 2–3 years." *Id.* at 1196.

Similarly, the published Columbia study articles rely on the cord blood test results to reach associational conclusions with respect to the following:

- "Highly exposed children ([those with] chlorpyrifos [cord blood] levels of >6.17 pg/g plasma) scored, on average, 6.5 points lower on the Bayley Psychomotor Development Index and 3.3 points lower on the Bayley Mental Development Index at 3 years of age compared with those with lower levels of exposure." Rauh *et al.* (2006), *Impact of Prenatal Chlorpyrifos Exposure on Neurodevelopment in the First 3 Years of Life Among Inner-City Children*, Pediatrics at 1, 10.

- "The high chlorpyrifos exposure group includes those with cord blood chlorpyrifos levels >6.17 pg/g, and the low group includes all those with lower levels." *Id.* at 19.

- "[B]irth weight decreased by 42.6 g (95% CI, –81.8 to –3.8, p = 0.03), and birth length decreased by 0.24 cm (95% CI, –0.47 to –0.01, p = 0.04) for each log unit increase in cord plasma chlorpyrifos levels." Whyatt *et al.* (2004), *Prenatal Insecticide Exposures and Birth Weight and Length among an Urban Minority Cohort,* 112 Environ Health Persp 1125, 1128–29.

- "Spearman's rank correlation coefficients were used to examine associations between pesticide levels in paired maternal and newborn blood samples." Whyatt *et al.*, *Biomarkers in assessing residential insecticide exposures during pregnancy and effects on fetal growth*, Toxicol. Appl. Pharmacol. 206: 246-254 at 248 (2005).

- "[A] highly significant inverse association between umbilical cord chlorpyrifos levels and both birth weight and birth length among infants in the current cohort born prior to U.S. EPA regulatory actions to phase out residential uses of the insecticide" was reported. *Id.* at 252.

- "[P]rior research has shown significant associations between chlorpyrifos concentrations in umbilical cord blood, and newborn birth weight and length (Whyatt *et al.* 2004) and child mental and motor development at age 36 months (Rauh *et al.* 2006)." Whyatt *et al.* (2009), *A Biomarker Validation Study of Prenatal Chlorpyrifos Exposure within an Inner-City Cohort during Pregnancy,* 117 Environ Health Persp 559, 565.

As discussed above, "these conclusions in the published articles for the Columbia study are invalid and unsupported because they are directly based on blood test results which are unreliable and invalid." Driver Decl. ¶ 18. For example, "[b]asing conclusions on a once-in-

time cord blood measurement is simply not scientifically justified because a once-in-time measurement is not representative of long-term exposure." *Id.* ¶ 14. Thus, "the unreliability and invalidity of the blood tests raises serious concerns about the accuracy of the classification of the blood test results into high (above 6.17 pg/g) and low (below 6.17 pg/g) exposure groups which, in turn, raises serious doubt about the claimed correlation between exposure groups and effects." *Id.* ¶ 17. Further, "[s]ince the blood test results for the Columbia cohort are not representative of true exposure, the threshold blood level (6.17 pg/g) above which effects are assigned to chlorpyrifos is meaningless." *Id.* In addition, "blood levels are very sensitive to time of sampling relative to time of last exposure (which is unknown), and are not a reliable biomarker for comparison of exposure in the individual." *Id.* In sum, "[b]ecause the Columbia study blood test results are not valid and reliable, the conclusions reached by the published studies based on the blood test results are not valid and reliable, especially for regulatory action." *Id.* ¶ 15.

iii. A New Analysis of Data from a Columbia Study Publication Casts Further Doubt on Columbia Study's Findings.

One of the most cited publications resulting from the Columbia study is Rauh *et al.* (2011). However, a recent analysis of data from the Rauh *et al.* (2011) publication conducted by TERA, attached as Appendix B, raises a number of scientific concerns about the reliability of the Columbia study's data and validity of the Columbia study's conclusions, similar to those raised by prior SAPs and numerous public commenters. Chief among those concerns is that, based on TERA's analysis of data that could be derived from figures and text of the Rauh *et al.* (2011) published article, certain data were missing and/or, because of the way they were graphically represented or plotted, may have impacted the trends observed and thus the conclusions drawn. For example, the TERA analysis found:

> Rauh et al. (2011) reported evidence of deficits in Working Memory Index and Full-Scale IQ in children at 7 years old as a function of prenatal CPF exposure. Although these data have not been made available, we were able to extract them in part through an analysis of Figures 1A and 1E of Rauh et al. (2011). This analysis uncovered a surprising fact. Data from approximately 35% of the 265 children described in the text of Rauh et al. (2011) were missing from Figure 1A; approximately 15% of these data were missing from Figure 1E. Although some of the missing data are possibly due to overlay of data points not observable in these published figures, such overlay cannot reasonably account for the extent of these missing data. Further, CCCEH correspondence to EPA admits that data of the four highest exposed children from Rauh et al. (2011) were removed from these figures because at least one data point "drastically impacts inference," *suggesting that the*

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> *statistical significance of these findings may have changed had these data been included.*
>
> The data extracted from the figures were analyzed in a number of ways, including a plot of data as response versus log dose, a typical toxicological and risk assessment approach. In contrast to Rauh et al. (2011), our analysis does not suggest any evidence of an effect on Full-Scale IQ (Figure 1E). We also find less of a negative association (reduction) in Working Memory Index (Figure 1A).

Appendix B at 13 (emphasis added). The TERA report's findings continue to demonstrate that there are significant scientific issues regarding the Columbia study's conclusions casting doubt on its suitability for use in regulatory decision-making, thus supporting EPA's Order denying the Petition.

iv. EPA Recently Recognized the Shortcomings of Epidemiology Studies in the Case of Fluoride.

EPA recognized that a single epidemiology study could not overcome robust animal toxicological data in its recent action denying a petition to prohibit the addition of fluoride to drinking water. *See* Fluoride Chemicals in Drinking Water; TSCA Section 21 Petition; Reasons for Agency Response, 82 Fed. Reg. 11,878 (Feb. 27, 2017). In denying the fluoride petition, EPA determined that the epidemiology studies urged in support of the petition had "significant limitations," including issues with study quality, uncontrolled confounders, and the lack of a dose-response relationship, such that the collective weight of evidence did not support granting the petition. For example, EPA stated that:

> [m]any of the human studies cited in the petition are cross-sectional in design, . . . are affected by antecedent-consequent bias . . . [and] are rarely suitable for the development of a dose-response relationship for risk assessment. . . . In epidemiology, studies using cross-sectional data are most often used to generate hypotheses that need to be further studied to determine whether a 'true' association is present. " 82 Fed. Reg. at 11,882, 11,884. Importantly, the Agency stated that a "*single epidemiological study* is not sufficient to 'corroborate' neurotoxic health effects, as stated in the petition." *Id.* at 11,884 (emphasis added). Finally, EPA observed that cross-sectional studies are "most useful for developing hypotheses about possible causal relationships between an exposure and a health effect, but are *rarely suitable for the development of a dose-response relationship for risk assessment.*

Id. at 11,882 (emphasis added).

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B. The Absence of the Raw Data Underlying the Epidemiology Studies Precludes Reliance on These Studies to Change the Current Regulatory Standard.

Principles of sound science dictate that the Agency must have access to all the raw data underlying the epidemiology studies before relying on them to make a regulatory decision. "Accessibility to the raw data would also further an evaluation of the exposure and health groupings, which may not be included in the peer review publications. . . . [T]his would permit an assessment of the reliability of the findings." Burns Decl. ¶ 25. Indeed, "[t]he lack of full accessibility to data and analytical results is a threat to scientifically-valid public health decision making." *Id.* ¶ 24. Moreover, "[a] systematic review of the published data is incomplete without having the complete analytical results to address more complex relationships that are not disclosed in the scientific epidemiology publications." *Id.* In addition, "[t]ransparency of the full scope of exposure data and outcomes, including those that show no effects, for the Columbia, Mt. Sinai and CHAMACOS studies, for example, would permit improved comparisons across studies." *Id.* ¶ 25.

But principles of sound science were not followed with respect to the epidemiology data. As set forth in the following chronology, and summarized on EPA's website, Chlorpyrifos: EPA's Seven Year Quest for Columbia's Raw Data, available at https://www.epa.gov/ingredients-used-pesticide-products/chlorpyrifos-epas-seven-year-quest-columbias-raw-data, EPA repeatedly recognized the need for the raw data and requested the raw data from the Columbia researchers, but did not receive any meaningful raw data in response to its requests:

- January 25, 2013: Letter from Steve Bradbury at EPA to PAN/NRDC, 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." Jan. 25, 2013 Ltr. from S. Bradbury to PAN/NRDC at 4, EPA-HQ-OPP-2007-1005-0097.

- April 2013: Meeting between representatives from OPP and Columbia researchers, during which the Columbia researchers did not agree to provide the raw data. Response to Comments at 19. EPA did not provide public notice of the meeting, and there are apparently no minutes or transcripts of the meeting. *See* DAS Response to RHHRA at 28. According to EPA's Response to Comments, the Agency learned during that meeting "that the kinds of exposure information (*e.g.*, timing of applications) requested were not collected by the investigators and therefore unavailable." *Id.* The Agency thus

"concluded that access to the raw data would not provide answers to the EPA's questions." *Id.* The Agency provided no explanation for this conclusion. Moreover, as further discussed in DAS's Response to the 2014 RHHRA, EPA's closed-door meeting with Columbia researchers did not result in the production of the raw data that EPA repeatedly said it needed to be able to use the Columbia study in the Agency's risk assessment. DAS Response to RHHRA at 28.

- Summer of 2015: Another Agency request for raw data, in response to which Dr. Dana Barr of Emory University gave the Agency "limited raw urine and blood data in her possession from the three cohorts." Response to Comments at 19. The Agency described these files as "not useful for the agency's current purpose of assessing risk from chlorpyrifos." *Id.*

- March 29, 2016: EPA released an Issue Paper prior to the April 2016 SAP, in which it provided "additional summary information on the blood biomonitoring data." *Id.* at 20. This summary information did not include raw data.

- April 19, 2016: Letter from Jack Housenger at EPA to Dr. Linda Fried at Columbia University, in which EPA again requested 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." Apr. 19, 2016 Ltr. from J. Housenger to Columbia University at 2, EPA-HQ-OPP-2008-0850-0871.

- August 1, 2016: Meeting between the Agency and Columbia researchers, during which Columbia "discussed the possibility of the EPA team visiting the data center to work with dataset in a secured enclave, however, EPA stressed that the transparency issue is not resolved by merely allowing access to EPA to the data and not making a dataset available for others to perform their own analysis." Chlorpyrifos Dataset Discussion: Columbia Center for Children's Environmental Health Mothers and Newborns Study at 2 (Aug. 1, 2016), EPA-HQ-OPP-2008-0850-0930.

- January 2, 2018: Letter from Richard Keigwin of EPA to Dr. Linda Fried at Columbia University, in which EPA once again requested dataset in order to address the "well-documented concerns on the reliance of this study in OPP's human health risk assessment for chlorpyrifos," and noting EPA's particular interest in "additional analyses of the available epidemiological studies using the actual data, including examining the log transformation for chlorpyrifos with WISC-IV scores."

- January 8, 2018: Email from Dr. Linda Fried to EPA stating that EPA needs to "clarify the information requests in [EPA's January 2, 2018] letter."

- No apparent progress in obtaining the raw data since EPA's January 2018 request.

This chronology illustrates that there are three categories of raw data at issue regarding the Columbia study: data that do not exist, data that are meaningless, and data that the Columbia researchers have refused to disclose.

As to the first category, EPA learned during a meeting with Columbia that data regarding pesticide product use among cohort participants were of "such poor quality"—essentially, non-existent—that they were of no use in assisting EPA "to better understand the pattern and frequency of organophosphate pesticide use among cohort participants." *See* 2014 RHHRA App. 6, at 387. In addition, the Columbia researchers informed EPA during that meeting that they had no data regarding the impact of postnatal exposures to polycyclic aromatic hydrocarbon ("PAH") on neurodevelopmental outcomes, which the 2012 SAP had identified as a concern because PAH is a "a ubiquitous air pollutant in inner-city areas such as NYC," and could have influenced the reported neurodevelopmental outcomes. *Id.* at 389. EPA's inability to have critical raw data underlying the Columbia study precluded EPA from testing the validity and reliability of the very controversial study results.

As to the second category, the information that Dr. Dana Barr disclosed to EPA was meaningless, and the "summary information" provided by the Columbia researchers to EPA and released prior to the 2016 SAP is insufficient to address concerns about the lack of raw data. This summary information appears to be the information referenced in the 2016 Chlorpyrifos Issue Paper, released prior to the April 2016 SAP. The "summary information" did not allay the 2016 SAP's concerns regarding unavailability of the raw data. Despite having this information at their disposal, the 2016 SAP nevertheless found numerous problems with the Columbia study's findings, and repeatedly criticized the lack of raw data. For example, the SAP stated that:

> [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.

2016 SAP Tr. at 494, 766 (emphasis added). EPA may not satisfy its obligation to make regulatory decisions for chlorpyrifos based on reliable data by relying on summary information deemed insufficient by the SAP.

As to the third category of raw data—data in Columbia's possession that EPA has been unable to obtain—as more fully discussed in DAS's January 2017 comments, any EPA reliance on the Columbia study without obtaining and reviewing the underlying raw data would be arbitrary and capricious, in violation of the Administrative Procedure Act ("APA"). *See* DAS Comments on 2016 RHHRA at 59–61. 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" under FFDCA § 408(b)(2)(D)(i), 21 U.S.C. § 346a(b)(2)(D)(i). *Id.* at 59. *See also* Seed Decl. ¶ 18 ("EPA is unable to assess the 'validity, completeness, and reliability of the data,' as it is statutorily required to do, without the raw data underlying the Columbia study and other epidemiology studies."). In addition, since registrants are required to provide EPA with access to data, Columbia's position creates a double standard. *See also* 2012 Bradbury Letter at 20 ("Registrant generated data, in response to FIFRA and FFDCA requirements, are conducted and evaluated in accordance with a series of internationally harmonized and scientifically peer-reviewed study protocols designed to maintain a high standard of scientific quality and reproducibility.").

DAS submitted a Freedom of Information Act ("FOIA") request to EPA for the raw data underlying the Columbia, Mt. Sinai and CHAMACOS epidemiology studies in December 2015, in response to which EPA released very limited files on March 1 and 2, 2016. However, "[n]one of the data files EPA provided for the Columbia, Mt. Sinai and CHAMACOS Studies in response to DAS's FOIA Request identify whether each study subject was the mother or the child. Such information is critically important to draw any conclusions from the data provided." Burns Decl. ¶ 34. What's more, only a few of the data files EPA provided appeared to be relevant to the Columbia study:

> [O]nly five of the 39 files provided by EPA in response to DAS's FOIA Request appear to have any relevance to the Columbia study. Of those five files, only two files appear to relate to chlorpyrifos levels in blood. Of those two files, one file has 141 unique study subjects and the other has 279 subjects. However, only 29 subjects in each of these two files have values for chlorpyrifos, representing 21% and 10% detection for each file, respectively. This number is vastly inconsistent with the number of blood samples purportedly having detectable levels of

> chlorpyrifos reported in published articles for the Columbia Study. . . . In sum, the data files provided by EPA do not come close to matching the sample sizes or percentages of chlorpyrifos detection reported in published articles for the Columbia study.

Id. ¶ 33.

In addition to these issues, the data files EPA released in response to the FOIA request "fail to provide any information regarding infant or maternal characteristics, or as to the results of any IQ or other neurodevelopment testing. Thus, it is impossible from the information provided by EPA to link any blood or urine samples or any alleged exposures to chlorpyrifos with neurodevelopment impacts." *Id.* ¶ 34. Moreover, "many of the data files are unlabeled and, thus, it is not known to what extent, if any, they are relevant to any of the epidemiology studies." *Id.* ¶ 35. "The deficiencies in the data EPA provided . . . make it impossible for an epidemiologist to draw any meaningful conclusions from the data or to replicate or otherwise support the published epidemiology studies which are purportedly based on the data." *Id.* ¶ 36. Thus, the data EPA provided in response to DAS's FOIA request were "meaningless and cannot be used to assess the accuracy and reliability of the epidemiology studies." *Id.* ¶ 30. The deficiencies in these data are such that "EPA does not have access to meaningful data underlying the Columbia, Mt. Sinai or CHAMACOS epidemiology studies." *Id.* ¶ 36.

In sum, none of the data EPA provided in response to DAS's FOIA request fall into the critical third category of data discussed above—data the Columbia researchers have refused to disclose that are necessary to fairly evaluate the study's conclusions. The data EPA did provide were incomplete and insufficient to assess the accuracy, reliability, and replicability of the Columbia, Mt. Sinai and CHAMACOS studies. Any reliance on the Columbia, Mt. Sinai and CHAMACOS studies in the face of these deficiencies in the raw data would not be consistent with sound and rational science. *See* Seed Decl. ¶ 18 ("Lack of access to raw data limits EPA's ability to assess the strength, accuracy, and generalizability of the Columbia study and other epidemiology studies. It also precludes replication of the research. These are cornerstones of robust scientific inquiry, which are absent from any effort to apply the epidemiology studies to chlorpyrifos."). The 2016 SAP was also deeply concerned that EPA did not have the raw data underlying the Columbia study. *See, e.g.,* 2016 SAP Tr. at 494. By any measure, the lack of access to the raw data for the epidemiology studies is inconsistent with science-based, transparent, and rigorous regulatory risk assessment and decision-making. This is especially true

given that these studies have been so heavily criticized and where the product at issue is of such importance to U.S. agriculture.

C. Even if the Cord Blood Results were Reliable and Valid, Several Factors Other than Exposure to Chlorpyrifos Can Explain the Effects Purportedly Observed in the Columbia Study.

Many factors can influence childhood development—both for better or worse—and could explain the effects purportedly observed in the Columbia study. The Columbia study does not address numerous confounding factors, calling into question the reliability of the study's findings. 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." Dr. Banner Comments to April 2016 SAP at 5, EPA-HQ-OPP-2016-0119 (Apr. 18, 2016) ("Dr. Banner Comments") (citing Lozoff, B. et al., *Long-term Developmental Outcome of Infants with Iron Deficiency*, New England Journal of Medicine, 325: 687-694, Sept. 1991; Hulthén, L. *Iron deficiency and cognition, Scandinavian Journal of Nutrition*, 47(3): 152-156, Feb. 2013).

Other important factors can profoundly influence childhood development, but were similarly unmeasured in the Columbia study. These include nutritional deficiencies (lack of iodine, vitamin D, vitamin B, as well as unhealthy diets, including excessive intake of sugar and fat); exposure to other materials in the environment (such as heavy metals and solvents); and other external stressors. For example, the published articles for the Columbia study "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." Dr. Banner Comments at 5 (citing Mills, R. et al., *Child Abuse and Neglect and Cognitive Function at 14 Years of Age: Findings From a Birth Cohort*, Pediatrics, 4-10, Dec. 6, 2010; Shonkoff, J.P. *et al.*, *The Lifelong Effects of Early Childhood Adversity and Toxic Stress*, Pediatrics, 129: e232—e246, Dec. 2011; LaGasse, L. *et al.*, *Prenatal Methamphetamine Exposure and Childhood Behavior Problems at 3 and 5 Years of Age*, Pediatrics, 681-88, Mar. 2012; Johnson, S. *et al.*, *The Science of Early Life Toxic Stress for Pediatric Practice and Advocacy*, Pediatrics, 319-327, Feb. 2013). In addition, studies have shown that maternal stress, bereavement, and depression—also unaccounted for by the Columbia study

investigators—can result in decrements in childhood neurodevelopment. (Mink, Kimmel, and Li 2012; Eaton et al. 2008).

"Perhaps most concerning, however, is the published articles' failure to accurately account for gestational age ('GA') as a confounding variable." *Id.* Indeed, "[n]ew 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." *Id.* at 5–6 (citing Espel, E.V. *et al.*, *Longer Gestation among Children Born Full Term Influences Cognitive and Motor Development*, PLOS ONE, Nov. 25, 2014). This research on gestational age "has led to changes in obstetrical practices during the time of the Columbia study." *Id.* at 6.

The Columbia study's authors do not explain how they calculated gestational age, yet:

> [t]he American College of Obstetrics and Gynecology ("ACOG") has guidelines for how to accurately measure gestational age for scientific research purposes, and cautions that, without a first-trimester ultrasound, a measure of gestational age is inaccurate by more than 5 days more than 40% of the time.[6] There is no indication that the Columbia Study investigators measured gestational age in accordance with ACOG guidelines, raising questions as to whether the Columbia Study data on this key covariate are scientifically sound. This is particularly concerning given that gestational age was a consistently significant covariate in the Perera (2003), Wyatt (2004), and Whyatt (2005) articles (indeed *the* strongest covariate in the 2003 Perera and 2004 Wyatt articles), and in light of new research suggesting that gestational age significantly influences neurodevelopmental outcomes.

Id. This failure to account for gestational age is especially concerning given that

> one of the Columbia Study's principal investigators, Dr. Virginia Rauh, co-authored an article in 2012 which found that gestational age was a key factor in predicting neurodevelopmental outcomes in children at eight years of age. This recognition clearly shows that gestational age is an important covariate, and yet the 2006 Rauh, *et al.* article, *Impact of Prenatal Chlorpyrifos Exposure on Neurodevelopment in the First 3 Years of Life Among Inner-City Children,* wholly fails to explain how the researchers measured gestational age. Moreover, in the model reported in the article, which claims to demonstrate an impact at 36 months, well-known covariates such as maternal IQ are not used. Without the underlying raw data and a more detailed explanation, it is impossible to assess whether these important confounding variables were accurately measured or used. The failure to explain how gestational age was measured also taints the sensitivity

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[6] Committee on Obstetric Practice, American Institute of Ultrasound in Medicine, Society for Maternal-Fetal Medicine, *Method for Estimating Due Date*, Comm. Op. No. 611, Oct. 2014.

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> analysis for the Columbia Study since the inaccuracy may be 40% or more. Even if the investigators accurately measured gestational age, the inclusion of study subjects with a gestational age as low as 30 weeks and weights as low as 1295 grams in Rauh, *et al.* 2011 casts doubt on the article's conclusions, in light of the demonstrated link between severe prematurity, gestational age and neurodevelopmental outcomes. Indeed, in this article gestational age does not appear to have been used in the model as a covariate. Since birthweight is generally a function of [gestational age], it is also critical to consider whether these babies fell within normative data for weight based on their [gestational age]. Growth that is both small for [gestational age] and large for gestational age poses neurodevelopment risks to the baby at the time of birth.

Id. at 6–7.

In sum, the above alternate explanations for the effects purportedly observed in the Columbia study need to be fully considered and accounted for when assessing the Columbia study.

D. Other Epidemiology Studies Do Not Support the Columbia Study's Findings.

Petitioners' Objections suggest that the CHAMACOS and Mt. Sinai studies lend credibility to the Columbia study, and that they "produced strongly convergent results." Petitioners' Objections at 8. The CHAMACOS and Mt. Sinai studies, however, assessed non-specific organophosphate metabolites in maternal urine and did not examine chlorpyrifos specifically. PHHRA at 31. *See also* 2008 SAP Minutes at 31 ("[M]etabolites not specific to chlorpyrifos exposure were measured and reported [in the CHAMACOS and Mt. Sinai studies], including those of other OPs and carbamates.").

As a preliminary matter, "there are significant problems with the design and execution of the CHAMACOS and Mt. Sinai studies that preclude a determination that the associations observed represent causal ones, and that the contributions of chance, bias and confounding cannot be ruled out." Declaration of Dr. Gregory Bond ("Bond Decl."), Attach. E. ¶ 27. *See also* 2008 SAP Minutes at 36 ("The Panel acknowledged that there are potential confounders and issues that reduce the utility of both the Mt. Sinai and [CHAMACOS] cohorts for risk assessment. For example, both studies measure organophosphate metabolites in urine but chlorpyrifos is not specifically measured."). Further, "[w]ith respect to infant health, the CHAMACOS and Mount Sinai studies estimated chlorpyrifos reported exposure using the metabolite urinary 3,5,6-trichloro-2-pyridinol (TCPy) in maternal urine prior to delivery. The

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data failed to show a statistically significant association of chlorpyrifos exposure and head circumference, birth weight or birth length." Burns Decl. ¶ 16. "Uniquely, the CHAMACOS study collected two urine samples during pregnancy and annually from the developing child. None of the urinary TCPy measures were reported to be associated with any adverse outcomes, including any neurodevelopmental outcomes measured." *Id.* ¶ 21. The CHAMACOS and Mt. Sinai studies have also not replicated hypotheses generated by the Columbia study:

> Working Memory (a domain of the Wechsler scale of intelligence (IQ) test) is another example for which other study results have not replicated the hypotheses generated by the Columbia study. While inversely associated with chlorpyrifos in plasma in the Columbia study children, Working Memory was not statistically associated with the urinary metabolite DEP in the CHAMACOS or Mt. Sinai studies. Two other similarly designed studies, (the Health Outcomes and Measures of the Environment Study conducted in Cincinnati, Ohio and the PELAGIE study in France), also did not replicate the Columbia study IQ findings.

Id. ¶ 19.

Moreover, the CHAMACOS and Mt. Sinai studies did not confirm the Columbia study's purported findings regarding attention-deficit hyperactivity disorder ("ADHD"):

> Among school age children, the Columbia study investigators reported that chlorpyrifos levels were associated with ADHD problems as measured with the Child Behavior Checklist ("CBCL") (OR = 6.50, 95% CI 1.09–38.69) (Rauh *et al.* 2006), but this association was not replicated in the CHAMACOS study using the mean of 2 prenatal urinary metabolite diethylphosphate (DEP) concentrations (OR = 0.59, 95% CI 0.21–1.68) (Eskenazi *et al.* 2007). The urinary metabolite, TCPy, that is more specific to chlorpyrifos than DEP, was not associated with any outcome in the CHAMACOS study. Further, the two publications of attention problems from the CHAMACOS study have mixed results across age groups of the children and different urinary organophosphate metabolites (Eskenazi *et al.* 2007, Marks *et al.* 2010). ADHD was not evaluated by the Mt. Sinai study. The CHAMACOS and Mt. Sinai studies therefore do not confirm the Columbia study's observations regarding ADHD.

Id. ¶ 17.

In sum, "[t]he neurodevelopmental outcomes have been overgeneralized across studies. The specific results are not reproduced from the other studies, which severely undermines any claim of a link between neurodevelopment effects and chlorpyrifos exposures." *Id.* ¶ 22. Thus, "[w]hen considering statistical testing in total across all studies, the other studies do not support or replicate the Columbia outcomes." *Id.* ¶ 20. Additionally, "[r]eliance on unreplicated epidemiology studies lacks scientific vigor, is contrary to Agency policies of data access and

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transparency in scientific decision-making, [and] disregards EPA's statutory obligations to make decisions based on valid, complete, and reliable scientific data[.]" *Id.* ¶ 10. Reliance on unreplicated studies also "ignores a critical, scientifically robust database of toxicological and other studies submitted to EPA showing that current uses of chlorpyrifos meet relevant safety standards." *Id.*

Prior FIFRA SAPs have identified limitations with the Columbia, CHAMACOS, and Mt. Sinai studies, For example, the 2012 SAP, convened to review the Agency's preliminary conclusions regarding a "weight-of-evidence" approach to integrating epidemiologic research in its assessment of neurodevelopmental outcomes, observed that the studies 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." 2012 SAP Minutes at 19; *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).

The 2008 SAP also identified deficiencies in the Columbia, CHAMACOS and Mt. Sinai epidemiological studies: "[o]ne of the key limitations of the epidemiological studies is that the exposure data were collected at single time point and lack information on the long-term exposure level and duration." 2008 SAP Minutes at 45. A second key limitation the Panel identified was that "the subjects in two of the cohort studies [Mt. Sinai and CHAMACOS] had multiple chemical exposures including multiple AChE-inhibiting insecticides[.]" *Id.*

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. Prueitt *et al.* (2011). In

short, the results of these birth cohort studies are conflicting and contradictory and do not implicate chlorpyrifos as a developmental toxicant. *See* Burns Decl. ¶ 20 ("When considering statistical testing in total across all studies, the [CHAMACOS and Mt. Sinai] studies do not support or replicate the Columbia outcomes.").

Indeed, as time has passed, more epidemiology studies have been conducted examining purported links between chlorpyrifos exposure and neurodevelopmental outcomes. Far from supporting the findings of the Columbia, CHAMACOS, and Mt. Sinai studies, this growing body of literature is confirming the opposite conclusion—that there is no consistent, clear evidence of associations between prenatal or childhood exposure to chlorpyrifos at levels below the current regulatory standard and adverse neurodevelopmental effects, including autism spectrum disorders ("ASD") and intelligence. *See, e.g.,* Schmidt *et al.* 2017 (no or non-significant association between chlorpyrifos exposure and ASD); Coker *et al.* 2017 and Gunier, Bradman, Harley, Kogut, *et al.* 2017 (no significant relationship between chlorpyrifos use and Full Scale IQ). Even a more recent publication by the CHAMACOS study investigators that examined residential proximity to chlorpyrifos use found no statistically significant associations between chlorpyrifos use and ASD-related traits. Sagiv *et al.* 2017.

VII. LEGAL FRAMEWORK

A. The FQPA and FFDCA, Including the Safety Factor Provision, Are Not Statutes Based on the Precautionary Principle.

Regulatory decisions under the FQPA and FFDCA, including the application of a safety factor, should be guided by two fundamental threshold principles. First, the food safety standard under the FFDCA and the FQPA is based on reasonable certainty of no harm, *not* absolute certainty of no harm. *See* Seed Decl. ¶ 16. While "a reasonable certainty of no harm" is not expressly defined in these two statutes, the term is described in the history of the 1958 Food Additives Amendments to the FFDCA with respect to the safety standard that the Food and Drug Administration is to apply in approving food additives under FFDCA § 409. In those amendments, Congress made it clear that the safety determination under the reasonable certainty of no harm standard does not require absolute proof of safety: "Safety requires proof of a reasonable certainty that no harm will result from the proposed use of an additive. It does not—and cannot—require proof beyond any possible doubt that no harm will result under any

conceivable circumstance." S. Rep. No. 2422, 85th Cong., 2d Sess. 6, *reprinted in* 1958 U.S.C.C.A.N. 5300, 5305; *see also* H.R. Rep. No. 2284, 85th Cong., 2d Sess. 4-5 (1958). FQPA established a single regulatory framework under FFDCA § 408 for pesticide residues in both raw and processed foods. *See* H.R. Rep. No.104-669, pt. 2, 104th Cong. 2d Sess. 43, *reprinted in* 1996 U.S.C.C.A.N. 1268, 1282; Food Quality Protection Act of 1996, Pub. L. No. 104-170, § 402, 110 Stat. 1489, 1513 (1996). Prior to that time, EPA was responsible for establishing any food additive regulations needed under FFDCA § 409 for pesticide residues in processed foods that exceeded the levels set in tolerances for raw agricultural commodities by EPA under FFDCA § 408.

Clear from the foregoing is that FQPA and FFDCA are not statutes based on the precautionary principle, under which all doubt must be exhausted before tolerances may be established for a crop protection product. Attempting to capture any doubt whatsoever to create "uncertainties" for purposes of applying an FQPA safety factor of 10X may be consistent with the precautionary principle, adopted by certain other countries, but it is not consistent with the statutory standard of reasonable certainty of no harm here in the United States.

B. The Agency Must Have Valid, Reliable Data to Make Regulatory Decisions, Including to Set a Safety Factor.

The second fundamental threshold principle that must guide the Agency is that its decisions must be based on valid, reliable data. This is especially true in deciding whether to apply a safety factor. Specifically:

- Tolerance revocations must be based on valid and reliable science – i.e., based on "the validity, completeness, and reliability of the available data from studies of the pesticide chemical and pesticide chemical residue[s]." FFDCA § 408(b)(2)(D)(i), 21 U.S.C. § 346a(b)(2)(D)(i). The application of a safety factor in order to revoke a tolerance is subject to no less a standard of validity, completeness, and reliability.

- "EPA uses available, *reliable* data when considering the need to raise, retain, modify, or remove the 10-fold additional safety factor." EPA, Progress Report: Implementing the Food Quality Protection Act (1999) ("EPA Progress Report") at 18 (emphasis added).

- Data that are not replicable, and in some cases not available, are not reliable. "In the context of epidemiology, reliability general[ly] refers to the ability to reproduce results . . . ." EPA, Draft Framework for Incorporating Human

Epidemiologic & Incident Data in Health Risk Assessment at 18 (Jan. 7, 2010) at 18 ("Draft Framework").

- Data that do not accurately reflect exposure are not valid. "In the context of epidemiology . . . validity generally refers to the extent that exposure estimates reflect true exposure levels." *Id.*[7]

Further, while "EPA considers all relevant data in its risk assessment analysis, [it] should act on only *reliable and valid* data. The same is true for FQPA safety factor determinations." Seed Decl. ¶ 14 (citing EPA, Determination of the Appropriate FQPA Safety Factor(s) in Tolerance Assessment ("Safety Factor Policy") at 29, 31 (2002) ("As part of the toxicological considerations, OPP evaluates potential pre- and postnatal toxicity on a case-by-case basis taking into account all pertinent information. . . . As in any weight-of-evidence approach, it is important to consider the *quality and adequacy of the data*, and the consistency of responses induced by the chemical across different studies.") (emphasis added)); EPA Progress Report, at 18.

In addition, tolerances cannot be revoked without valid and reliable data because registrants have a protectable property interest in their registration. *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 08-01814 MHP, at 4 (N.D. Cal. July 8, 2008), ECF No. 43 ("The registrations involved here are essentially government licenses to produce,

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[7] EPA has also recognized the need for *valid, reliable* data in other contexts. For example, FIFRA's interim administrative review provision states that "the Administrator may not initiate a public interim administrative review process to develop a risk-benefit evaluation of the ingredients of a pesticide or any of its uses prior to initiating a formal action to cancel, suspend, or deny registration of such pesticide, required under this subchapter, *unless such interim administrative process is based on a validated test or other significant evidence* raising prudent concerns of unreasonable adverse risk to man or to the environment." 7 U.S.C. § 136a(c)(8) (emphasis added). The term "validated test" is defined as "a test conducted and evaluated in a manner consistent with accepted scientific procedures," and the term "other significant evidence" is defined as "evidence that relates to the uses of a pesticide and their adverse risk to man or to the environment." Pesticides/Interim Administrative Reviews, Proposed Definitions of "Validated Test" and "Other Significant Evidence," 44 Fed. Reg. 9626, 9627 (Feb. 14, 1979).

distribute and sell pesticides . . . [and] therefore constitute property[.]"). It is therefore essential that the Agency have valid and reliable data and conduct a thorough, science-based assessment for its regulatory decision-making.

C. EPA Addressed the FQPA's 10X Safety Factor Provision by Relying on a Robust Set of Animal Toxicological Data that Accounted for Children's Susceptibility.

Starting in 2014 with the RHHRA, EPA has suggested that it should raise the FQPA safety factor to 10X due to "uncertainty" derived by the Agency on the basis of the Columbia study and other epidemiology studies. But that approach is not consistent with Agency guidance on setting safety factors. EPA's Safety Factor Policy states that "[i]f toxicity data indicate no concern for pre- and postnatal toxicity, then the risk assessor should treat the presumption for use of the default 10X safety factor as having been obviated with respect to the potential for pre- and postnatal toxicity." Safety Factor Policy at 29. Additionally, EPA "does not establish FQPA safety factors for chemicals based on speculation or the elimination of all possible doubt." Seed Decl. ¶ 16. Here, the Agency has "toxicity data in the form of robust and reliable animal studies which address children's susceptibility and showed no concern for pre- and postnatal toxicity." *Id* ¶ 23. The Agency therefore set a safety factor of 1X for chlorpyrifos in its 2006 Cumulative Risk Assessment. EPA thus addressed the FQPA 10X safety factor provision with a robust and reliable set of animal data. Due to their significant limitations and deficiencies, the epidemiology studies do not change this outcome.

It is clear from the FQPA that EPA cannot raise the safety factor to 10X based on data that do not meet standards of reliability and validity when the Agency has already made a safety factor determination based on a robust and reliable set of animal data that account for children's susceptibility. Seed Decl. ¶ 23 ("Studies like the Columbia study that are not reliable for regulatory decision-making cannot be used to increase that 1X safety factor determination.").

When Congress passed the FQPA, it did not contemplate that unreliable epidemiology studies could be used to upset the Agency's safety factor determination that was based on a complete, reliable set of animal toxicology data that accounts for children's susceptibility. "[T]he focus of EPA's 10X safety factor determination has been on the robustness and completeness of the animal toxicology data set." *Id.* ¶ 21. Indeed, DAS is not aware of any other chemical for which EPA had a complete, reliable animal toxicology data set supporting an FQPA safety factor below 10X, as is the case for chlorpyrifos, but relied on epidemiology

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studies having numerous issues regarding validity and reliability and for which the underlying raw data were unavailable to drive up the FQPA safety factor to 10X. *See id.* ¶ 23. Here, "the epidemiology studies that are currently available with respect to chlorpyrifos exposure and possible neurodevelopmental effects are not valid and reliable for purposes of showing that there is an exposure hazard for chlorpyrifos that is not already accounted for in the current regulatory standard, and cannot be used to increase the Agency's 1X safety factor determination." *Id.* ¶ 4. The toxicological studies advanced as supporting epidemiology research linking chlorpyrifos exposure and neurodevelopmental effects are similarly not reliable as a basis for increasing the Agency's safety factor determination. *See, e.g.,* Section V.A., *supra*; Appendix A.

D. EPA Cannot Rely on the Epidemiology Studies for Regulatory Decision-Making without the Underlying Raw Data.

As detailed in DAS's prior comments, EPA's reliance on the Columbia study (or any of the additional epidemiology studies) without access to the raw data would violate principles of sound science, Agency policies regarding data access and transparency, and SAP guidance, and would be arbitrary and capricious. *See, e.g.,* DAS Comments on 2016 RHHRA at 59–61. In particular, OMB Circular A-110 mandates the public disclosure of data underlying federally funded studies used to develop agency action that has the force and effect of law. Moreover, without all of the raw data from the Columbia study and other epidemiology studies upon which the Agency may rely, EPA could not 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). In addition, without the underlying data from the Columbia study and other epidemiology studies, results cannot be replicated and are therefore not reliable under the FFDCA. *See* DAS Comments on 2016 RHHRA, § VII.

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).

It has been suggested in the past that *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) stand for the proposition that EPA 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.[8]

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[8] Indeed, if EPA were to shift course again and proceed with revoking all tolerances and canceling chlorpyrifos registrations, its failure to disclose the raw data on which its proposed rule was based would be procedurally deficient. *See Shands Jacksonville Med. Ctr. v. Burwell*, 139 F. Supp. 3d 240 (D.D.C. 2015) (observing that "it is especially important for the agency to identify and make available technical studies and data that it has employed") (quoting *Conn. Light & Power Co. v. Nuclear Reg. Comm'n*, 673 F.2d 525, 530 (D.C. Cir. 1982)); *Wash. Trollers Ass'n v. Kreps*, 645 F.2d 684, 686 (9th Cir. 1981) (agency must disclose data underlying proposed regulation so that public can provide meaningful comment).

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VIII. DAS'S SPECIFIC RESPONSES TO THE OBJECTIONS

As set forth above, the Agency has a robust set of reliable animal toxicological data that support the current regulatory standard for chlorpyrifos. Petitioners and the States raise additional specific objections, set forth below, none of which are supported by the applicable law, the scientific evidence, or the regulatory history for chlorpyrifos.

A. The Objections Misrepresent the Scientific and Regulatory History for Chlorpyrifos.

The Objections contain numerous misstatements and inaccuracies regarding the scientific and regulatory history for chlorpyrifos. As is evident from Sections V–VI, *supra*, (and DAS's prior comments), the Objections are simply flat-out wrong to suggest that the lack of safety for chlorpyrifos at exposure levels below the current regulatory standard is uncontroverted. To the contrary, FQPA's standard of reasonable certainty of no harm continues to be met by a robust, reliable, and valid dataset.

Petitioners' misrepresent the scientific record, cherry-picking statements that they assert support their claims and insisting incorrectly that the science is beyond dispute and that only "purely legal issues" are presented in their Objections. Petitioners also present the Columbia and other epidemiology studies as if they were new evidence, misleadingly referring to the "growing body of published scientific research" allegedly linking chlorpyrifos exposure with adverse neurodevelopmental outcomes. Petitioners' Objections at 8. But Columbia researchers started publishing in 2002 on exposure, with the infant outcome studies first appearing in 2004. EPA was thus aware of the Columbia study results when it reaffirmed its confidence in the current regulatory standard, and the complete database of animal toxicology studies underpinning that standard, several times, including as recently as March 2015. *See* PHHRA at 7 ("[C]holinesterase inhibition (ChEI) provides the most sensitive dose-response information for deriving points of departure for chlorpyrifos."); *id.* at 22, 36 ("The toxicological database for chlorpyrifos is extensive and is adequate to support the registration review."); 2014 RHHRA at 24 ("[Acetylcholinesterase] inhibition remains the most robust quantitative dose response data and thus continues to be the critical effect for the quantitative risk assessment."); EPA's March 26, 2015 Ltr. to PAN/NRDC, *PANNA II*, ECF No. 14, Attach 1 at 3. SAPs convened during that time period also supported the continued use of cholinesterase inhibition as the PoD.

In another misstatement, the Objections assert that the 2011 PHHRA found that "chlorpyrifos likely played a role in long term neurological effects from early exposures that were evaluated in the epidemiology studies." Petitioners' Objections at 15. That is incorrect. Neither the PHHRA nor the PHHRA Reader's Guide made such a statement.

The Objections also repeatedly and wrongly assert that EPA has made negative "findings" and "determinations" about the safety of chlorpyrifos. In fact, however, EPA has made no final, reviewable determinations regarding the safety of chlorpyrifos that have changed its 2006 final determination that the use of chlorpyrifos consistent with the current regulatory standard presents a reasonable certainty of no harm. *See* EPA, Finalization of Interim Reregistration Eligibility Decision (IREDs) and Interim Tolerance Reassessment and Risk Management Decisions (TREDs) for the Organophosphate Pesticides, and Completion of the Tolerance Reassessment and Reregistration Eligibility Process for the Organophosphate Pesticides, July 31, 2006 ("EPA has concluded, after completing its assessment of the cumulative risk associated with exposures to all of the OPs, that . . . the pesticide tolerances [for chlorpyrifos] . . . meet the safety standard under Section 408(b)(2) of the FFDCA"). This is the only final determination regarding the safety of chlorpyrifos tolerances that is currently in effect, as EPA's Registration Review of chlorpyrifos is ongoing. *See New York v. EPA*, 350 F. Supp. 2d 429, 435–36 (S.D.N.Y. 2004) ("[T]he issuance of a RED, whether it be one revoking, modifying, or leaving in place a tolerance, constitutes the agency's final determination, at the conclusion of a statutorily mandated review process, on the safety of the tolerance in question."), *aff'd sub nom. Nat. Res. Def. Council v. Johnson*, 461 F.3d 164 (2d Cir. 2006).

Though EPA complied with the Ninth Circuit's mandamus order when it denied the Petition, EPA has not yet taken any final agency action subject to judicial review that departs from its 2006 final determination. To the contrary, the statements EPA made prior to its Petition denial were part of the Agency's non-binding, deliberative process. In particular, EPA's March 2015 letter to Petitioners indicating the Agency's intention to deny the Petition, its October 2015 Proposed Rule, and its 2014 and 2016 risk assessment proposals with respect to neurodevelopmental impacts purportedly linked to chlorpyrifos exposure represent the Agency's deliberations on potential agency action but are not final decisions that are binding on the Agency. *See Nat'l Ass'n of Home Builders v. Defs. of Wildlife*, 551 U.S. 644, 658–59 (2007) ("[F]ederal courts ordinarily are empowered to review only an agency's final action, and the fact

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that [an agency's] preliminary determination . . . is later overruled at a higher level within the agency does not render the decisionmaking process arbitrary and capricious.").

EPA has itself acknowledged the tentative, non-binding nature of its recent risk assessments with respect to chlorpyrifos. EPA Order at 16,590 ("EPA has three times presented *approaches* and *proposals* to the FIFRA SAP for evaluating [the] recent epidemiologic data.") (emphasis added). And EPA has in the past characterized pesticide risk assessments as preliminary, interim steps in the agency decision-making process. For example, in a 2001 lawsuit against the Agency, EPA sought dismissal of a challenge to EPA's cancer reassessment for pyrethins and EPA's not yet completed risk assessment for dioxin on the grounds that "[b]oth the challenged actions are just interim steps in ongoing agency processes" and "not 'final agency action' so as to be reviewable under the [APA]." *See, e.g.,* Mot. Filed by Fed. Def. to Dismiss Compl. for Lack of Jurisdiction, *Tozzi v. EPA*, No. 1:00-CV-02604 (D.D.C. Feb. 5, 2001), ECF No. 14. EPA observed that a number of regulatory and scientific issues related to pyrethins remained "in flux" and that its evaluation of human health risks of dioxin and consideration of public comments on its latest assessment were ongoing.

It is well-established that agencies may depart from prior proposals and assessments in the course of the regulatory decision-making process. *See Nw. Coal. for Alts. to Pesticides (NCAP) v. EPA*, 544 F.3d 1043, 1051 (9th Cir. 2008) (according deference to EPA's decision to await results of certain studies before establishing pesticide tolerances, even though this departed from the Agency's prior position); *Ctr. for Biological Diversity v. U.S. Forest Serv.*, No. CV-09-8116-PHX-FJM, 2009 WL 3740732, at *3 (D. Ariz. Nov. 5, 2009), *aff'd*, 408 F. App'x 64 (9th Cir. 2011) (upholding agency decision to depart from preliminary biological assessments regarding a forest fire project, reasoning that "[r]efinement and modifications of positions are a natural part of the deliberative process" and an "agency is entitled to change its mind"). Moreover, EPA's Order is hardly the abrupt 180 degree turnabout Petitioners seek to portray, given that as recently as March 2015 EPA notified the Ninth Circuit and the Petitioners of its intention to *deny* the Petition. In fact, it was EPA's June 2015 status report in the mandamus action announcing its intention to grant the petition and subsequent Proposed Rule—which proposed to replace decades of established science with a single, unreplicated epidemiology study as the basis for major regulatory action—that marked an unprecedented sea change in the Agency's decision-making process. *See* Status Rep., No. 14-72794, ECF No. 20. Simply stated,

the EPA statements recounted by the Objectors were tentative, non-binding statements that were not "sufficiently final [for the Agency] to demand compliance with [an] announced position," *Ciba-Geigy Corp. v. EPA*, 801 F.2d 430, 436 (D.C. Cir. 1986).

EPA's Order recognizes that its assessments and proposals during 2015–2016 were based on inconclusive science that was not sufficient to support final regulatory action. Petitioners' assertions that EPA has already made conclusive "findings" ignore the non-binding, tentative nature of EPA's deliberative process. Objectors, through the administrative process provided under FFDCA and FIFRA for resolution of their objections, "still enjoy[] an opportunity to convince the agency to change its mind." *Id.*

The Objections ignore that EPA's Order is also consistent with recent findings in the European Union and Australia. *See, e.g.,* APVMA, Reconsideration of Chlorpyrifos, *supra* at 5. Notably, the EFSA as recently as 2014 conducted a reevaluation of chlorpyrifos-related toxicology and selection of regulatory endpoints for human health 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, which was less conservative than use of Red Blood Cell cholinesterase inhibition. 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. PPR Panel Minutes at 9. This action thus aligned the endpoint with the RBC ChE inhibition endpoint currently used by EPA.

As part of the European Commission reevaluation of chlorpyrifos toxicology and human health (EFSA, 2014), EFSA paid particular attention to several epidemiology studies, including the Columbia study (Lovasi *et al.* 2011; Rauh *et al.* 2012; Rauh *et al.* 2011; Rauh *et al.* 2006;

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Whyatt *et al.* 2009; Whyatt *et al.* 2007; Whyatt *et al.* 2004), the Mt. Sinai study (Berkowitz *et al.* 2004; Engel *et al.* 2007; Engel *et al.* 2011), and the CHAMACOS study (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 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. Moreover, university researchers (Ntzani *et al.* 2013), under contract with EFSA reviewed the epidemiology studies published since 2006. Ntzani *et al., Literature review on epidemiological studies linking exposure to pesticides and health effects*, EFSA supporting publication 2013:EN-497. They concluded there is no evidence to suggest an association between pesticide exposure, including chlorpyrifos, and neurodevelopmental effects.

B. Chlorpyrifos Does Not Present a Volatilization Risk at the Current Regulatory Standard.

Petitioners claim that there is "extensive evidence that drift is reaching people and causing poisonings" and "EPA . . . found that chlorpyrifos can drift in harmful amounts." Petitioners' Objections at 12. Petitioners further assert that the DAS volatilization studies do not support EPA's finding of no risk from volatilization. *Id.* at 13–14.

However, EPA's 2014 Revised Human Health Risk Assessment ("RHHRA"), at 10, stated that "there are no anticipated risks of concern from exposure to the volatilization of either chlorpyrifos or chlorpyrifos oxon:"

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> EPA lacked chlorpyrifos vapor toxicity data at the time it conducted the preliminary volatilization assessment in 2013. Following the release of the preliminary volatilization assessment, Dow AgroSciences LLC conducted . . . high quality nose-only vapor phase inhalation toxicity studies for both chlorpyrifos and chlorpyrifos-oxon to address this uncertainty. . . . Because these new studies demonstrated that no toxicity occurred even at the saturation concentration, which is the highest physically achievable concentration, then there is no anticipated risks of concern from exposure to the volatilization of either chlorpyrifos or chlorpyrifos oxon. In June 2014, the January 2013 volatilization assessment was revised to reflect these findings.

RHHRA at 83–84.

Petitioners have presented no evidence that chlorpyrifos poses risks from volatilization at the current regulatory standard,[9] or that DAS's volatilization studies do not support the Agency's prior findings. Indeed, in its 2013 Preliminary Evaluation of the Potential Risks from Volatilization for chlorpyrifos, the Agency stated that "the available data are insufficient to directly link respiratory effects to chlorpyrifos volatilization exposure." EPA, Chlorpyrifos; Preliminary Evaluation of the Potential Risks from Volatilization, Docket EPA-HQ-OPP-2008-0850-0114 at 20 (Jan. 31, 2013).

Petitioners also wrongly assert that there was a "lack of controls in the [DAS] study that demonstrated that the experiment was capable of successfully producing or detecting cholinesterase inhibition. Without such controls, the study results cannot be interpreted or used to claim that chlorpyrifos volatilization does not produce cholinesterase inhibition." Petitioners' Objections at 14. Petitioners' assertion is incorrect—the studies show tissue-specific cholinesterase activity, which is consistent across both the chlorpyrifos and oxon vapor studies. There were controls in both studies, and the studies measured the blood levels of the parent and the metabolite TCP, which proves that the animals were exposed and that the inhaled parent molecule was bioavailable. Further, the data from the chlorpyrifos aerosol study clearly shows that the same validated cholinesterase activity assay can detect inhibition if the systemic dose is

[9] Petitioners cite to an incident in which farmworkers in Kern County, California, were allegedly "poisoned" by chlorpyrifos exposure as a result of a company's spraying of a product containing chlorpyrifos on a nearby farm. However, investigators found that the company had improperly sprayed the chemical because it used a nozzle that violated the pesticide's label requirements. *See* https://ww2.kqed.org/news/2017/08/08/produce-company-behind-popular-cuties-fined-over-pesticide-drift/.

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sufficient to inhibit ChEI. Finally, the volatilization studies were conducted according to Good Laboratory Practices.

Petitioners claim that volatilization rates could differ based on differing environmental conditions, but the toxicity study was done using the maximum amount of chlorpyrifos. Thus, the air could hold at saturation regardless of the rate of any release into the air, and rate of flux from the soil is therefore irrelevant.

Finally, any volatilization loss off site from treated fields would be expected to be low and very temporary and would not represent a chronic exposure or even significant acute exposure. Air monitoring data collected in California by the state supports this conclusion.

C. Petitioners Misrepresent the 2008 SAP's Findings.

Petitioners misleadingly suggest that the 2008 "SAP confirmed EPA's conclusion that early life exposures to chlorpyrifos pose a risk of long-lasting, adverse cognitive, behavioral, and motor impairments." Petitioners' Objections at 2; *see also id.* at 14–16. But the 2008 SAP did not make a conclusive determination about chlorpyrifos' potential for causing neurodevelopmental effects. Petitioners also fail to mention that the 2008 SAP found that "cholinesterase inhibition should continue to be used for PoD until, at such time[,] an alternative mode of action is identified and validated." 2008 SAP Minutes at 12. The Panel further stated that the Columbia, Mt. Sinai, and CHAMACOS epidemiology studies "should not be considered as the principal basis for characterization of the PoD." *Id.*

In addition, while Petitioners state that "[t]he Panel found that 'chlorpyrifos likely played a role in the birth and neurodevelopmental outcomes noted in the three cohort studies,'" Petitioners' Objections at 14, they fail to acknowledge that the Panel went on to state that "*it cannot be stated that chlorpyrifos is the sole contributor to the observed outcomes*," 2008 SAP Minutes at 37 (emphasis added). The Panel also stated that "[c]onfounding factors in the Mt. Sinai and [CHAMACOS] studies, particularly the fact that exposures were based on OP and carbamate metabolites and that chlorpyrifos was not specifically measured, reduce their utility in a quantitative context for risk assessment." *Id.* at 12–13. Finally, due to the limitations in the CHAMACOS, Columbia, and Mt. Sinai studies, the Panel discouraged EPA from using the studies quantitatively in risk assessment. Specifically, the Panel "agreed with the Agency that there were limitations in the three epidemiological studies that precluded them from being used to directly derive the PoD or the uncertainty factor." *Id.* at 46.

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D. Petitioners Rely on a Declaration by Dr. Philip Landrigan that is Replete With Errors and Incorrect Assumptions.

Petitioners cite to a declaration by Dr. Philip Landrigan to support their argument that chlorpyrifos purportedly causes neurodevelopmental effects in children at levels of exposure below the current regulatory standard. Petitioners' Objections at 4 n.3. Dr. Landrigan, in turn, cites to an article by Dr. David Bellinger for the proposition that exposure to organophosphate pesticides has led to "a total loss of 16.9 million IQ points." Landrigan Decl. ¶ 36.

There are numerous flaws in Dr. Landrigan's declaration: first, Dr. Landrigan wrongly asserts that the human studies were conducted outside of the United States and were "criticized for not meeting the informed consent standards that would be required in the US and also for scientific deficiencies." Landrigan Decl. ¶ 27. But Dr. Landrigan's declaration does not identify the human studies he is criticizing, and two of the human studies relevant to the PBPK model that Dr. Landrigan references were in fact conducted in the United States: the Nolan (1982) study was conducted at Dow Chemical in Midland, Michigan, and the Kisicki (1999) study was conducted by MDS Harris Laboratories (now Celerion Lab) in Lincoln, Nebraska. Moreover, both human volunteer studies were approved by the US EPA Human Subjects Review Board ("HSRB"). The EPA HSRB 2009 review of the Nolan *et al.* (1982) study states that "[t]he Board concurred with the Agency's assessment that there was neither clear and convincing evidence that the study was fundamentally unethical, nor clear and convincing evidence that the study was significantly deficient relative to the ethical standards prevailing at the time the Nolan et al. (1982) study was conducted." *Id.* at 2. In addition, the Supplemental EPA ethics review of the Kisicki (1999) study from December 2014 states that

> the study was not deficient relative to the prevailing ethical standards in a way that placed participants at increased risk of harm or impaired their informed consent. Therefore, reliance on this study is not prohibited by 40 CFR §26.1704(2). This conclusion agrees with the recommendations of the HSRB in its October 2009 report.

EPA, Supplemental Ethics Review of Chlorpyrifos Human Toxicity Study by Kisicki *et al.* (Dec. 12, 2014) at 6.

Dr. Landrigan also incorrectly claims that "[a] key policy breakthrough occurred over the past three decades with the discovery that children are far more sensitive than adults to toxic chemicals in the environment." Landrigan Decl. ¶ 9. "To the contrary, most scientists agree that

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the evidence actually shows that sometimes children are more, the same or even less sensitive to the effects of exposure to chemicals—it depends on the chemical, the effect and other factors." Bond Decl. ¶ 20 (citing National Academy of Sciences Report: Pesticides in the Diets of Infants and Children (1993), https://www.nap.edu/read/2126/chapter/2 (last visited Sept. 24, 2017) ("Children may be more sensitive or less sensitive than adults, depending on the pesticide to which they are exposed.")). In addition, Dr. Landrigan does not cite any empirical data or science to back up his assertion that exposure to pesticides can lead to permanent brain injury during the sensitive life stages.

Dr. Landrigan additionally contends that "[i]n the Columbia study, the degree of reduction in head circumference was proportional to the degree of maternal exposure to chlorpyrifos during pregnancy," and that "[t]he impact of chlorpyrifos on head circumference was no longer observed after the ban on residential application of chlorpyrifos was imposed." *Id.* ¶ 22. He does not present any proof for this. In fact, "the Columbia study authors found no association between head circumference and chlorpyrifos exposure (Whyatt *et al.* 2004)." Bond Decl. ¶ 29. Dr. Landrigan also erroneously asserts that the three epidemiology studies "found damage to children's brains from exposures to chlorpyrifos that produced no or less than 1% red-blood cell cholinesterase inhibition." Landrigan Decl. ¶ 24. However, "[t]here is no basis in these studies to support that conclusion, and authoritative bodies around the world have concluded the 10% cholinesterase inhibition is the appropriate regulatory standard for chlorpyrifos safety." Bond Decl. ¶ 29.

Further, Dr. Landrigan wrongly characterizes the discontinuation of residential uses of chlorpyrifos as a "ban." Landrigan Decl. ¶ 22. In fact, the Federal Register Notice announcing the discontinuation stated that registrants and EPA had agreed to "several voluntary measures" to reduce chlorpyrifos exposure. Chlorpyrifos; Cancellation Order, 65 Fed. Reg. 76,233, 76,234 (Dec. 6, 2000). Nowhere in that announcement did EPA characterize the discontinuation as a "ban." And, the agreement to discontinue residential uses was not reached because EPA deemed the uses unsafe, but because EPA changed key science policies under the FQPA, and applied standards far more restrictive than those historically established. *See* Chlorpyrifos Revised Risk Assessment and Agreement with Registrants (June 2000) at 1 ("The Food Quality Protection Act, enacted in 1996, sets a more stringent safety standard for most pesticides and offers special protection for children."). EPA did not find that these chlorpyrifos uses posed an imminent

hazard, and the phase-out of sales for affected residential use products was allowed to occur over a five-year period.

Dr. Landrigan also claims that the Columbia, CHAMACOS, and Mt. Sinai studies "produced strongly convergent results," Landrigan Decl. ¶ 22, and that all three studies showed reductions in motor function, decreases in working and visual memory, processing speed, verbal comprehension, perceptual reasoning and diminished IQ, *id.* ¶ 23. This is untrue:

> Contrary to Dr. Landrigan's view, a 2011 weight of evidence evaluation integrating the results of available epidemiology studies (including the Columbia study) and laboratory animal studies concluded that "[t]he weight of the available evidence more strongly indicates that a causal association between chlorpyrifos exposure and neurodevelopmental effects in the absence of AChE inhibition in the brain is not plausible for humans, and the few positive associations observed in epidemiology studies would be attributed to alternative explanations." Prueitt *et al.*, Hypothesis-based weight-of-evidence evaluation of the neurodevelopmental effects of chlorpyrifos. Crit Rev Toxicol 41(10): 822-903 (2011). *See also* Reiss *et al.*, *A review of epidemiologic studies of low-level exposures to organophosphorus insecticides in non-occupational populations*, Critical Reviews in Tox., 145:7, 531, 638 (2015); Burns *et al.*, *Pesticide Exposure and Neurodevelopmental Outcomes: Review of the Epidemiologic and Animal Studies,* Journal of Tox. and Environ Health, Part B, 16:127-283 (2013). . . . In addition, recent evidence from two similarly designed and executed studies, one in Ohio and the other in France, found no associations between urinary DAP levels and lower childhood intelligence scores (Cartier *et al.* 2016, Donauer *et al.* 2016). The weight of all the epidemiology evidence (human and animal) therefore does not prove a cause and effect connection between levels of chlorpyrifos exposure below the current regulatory standard and adverse human effects.

Bond Decl. ¶¶ 27–28.

Dr. Landrigan does not define "low-dose" when he states that neurobehavioral effects were purportedly observed in animal studies after "low-dose perinatal chlorpyrifos exposure." Landrigan Decl. ¶ 19. Nor does he put "low-dose" into the context of actual human exposure. He also makes incorrect statements about inter- and intra-species safety factors. *See id.* ¶ 27.

With respect to Dr. Landrigan's reliance on Dr. Bellinger's article for the proposition that exposure to organophosphate pesticides has led to "a total loss of 16.9 million IQ points," Landrigan Decl. ¶ 36, there is no indication that Dr. Bellinger reviewed the Columbia study or any other studies pertaining to chlorpyrifos. *See* Bond Decl. ¶ 43 ("[Dr. Bellinger] did not conduct a state of the art systematic review of the evidence, but instead took at face value the selected findings from published studies of two small groups of children—the CHAMACOS and

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Mount Sinai birth cohort —which . . . have inconsistent results and have been significantly criticized for having design and executions errors."). The publication itself recognizes the limitations in its own conclusions due to assumptions made and the lack of available data. *See* Bellinger (2012), *A Strategy for Comparing the Contributions of Environmental Chemicals and Other Risk Factors to Neurodevelopment of Children*, 120 Environ Health Persp 501–07 at 506 ("Any effort to compare the neurodevelopmental burden associated with different risk factors is limited by the data available and the assumptions required."). The Columbia, CHAMACOS, and Mt. Sinai studies simply do not establish a causal effect between exposure to organophosphates and loss of IQ points. *See* Bond Decl. ¶ 43 (Dr. Bellinger "also proceeded to confuse mere correlation with causation by not systematically evaluating the studies for bias or checking to see if the criteria for causation were satisfied."). In addition, Dr. Bellinger's entire analysis is based on an alleged correlation between DAP levels and loss of IQ points, even though "it is not scientifically valid to rely on DAP levels detected in urine to conclude that exposure to chlorpyrifos has occurred." Burns Decl. ¶ 23. Importantly, "DAP is not specific to chlorpyrifos. Thus, the specific OP pesticides contributing to urinary DAP levels may be different for the California farm worker participants (CHAMACOS) and the urban New York City participants (Mt. Sinai Study)." *Id.* Further, "the sample results may reflect contacts with one or more of the parent pesticide OPs that metabolize to DAP, or may reflect its environmental residue metabolite that then metabolized to DAP." *Id.* Thus, "DAP levels should not be used for interpreting outcomes for an individual pesticide." *Id.*

Despite the inconsistencies in the epidemiology studies, "Dr. Bellinger did not engage in any critical review of either [the Mt. Sinai or CHAMACOS] study, but simply assumed that the associations that were reported were indeed causal. Such an assumption was not justified." Bond Decl. ¶ 38. In sum, Petitioners' claim that chlorpyrifos exposure has led to a loss of IQ points is unsubstantiated because "Dr. Bellinger's article is not specific to chlorpyrifos, failed to adequately analyze the CHAMACOS and Mt. Sinai epidemiology studies and drew unfounded conclusions about the studies' findings, and ignored robust animal toxicology data that support the current regulatory standard for chlorpyrifos." *Id.* ¶ 44.

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E. Petitioners Wrongly Assert that EPA has Found Unsafe Drinking Water Contamination from Chlorpyrifos.

Petitioners and the States cite to EPA's drinking water assessment as further evidence that chlorpyrifos is purportedly unsafe. Petitioners' Objections at 31; States' Objections at 8. But, as described in DAS's prior comments, EPA's drinking water assessment remains only a screening-level evaluation and is therefore incomplete. *See* DAS Comments on 2016 RHHRA at 72-85. The Agency's drinking water assessment is inadequate for purposes of conducting a human health risk assessment, as it is merely a slightly modified screening-level assessment. The input parameterization of the modeling carried out in the April 2016 Refined Drinking Water Assessment ("RDWA") (EPA-HQ-OPP-2015-0653-0437) employs a series of compounding conservative factors, especially related to the intensity of product use.

The Agency's statement that "if the chlorpyrifos use profile changes, [the data] are provided to quickly facilitate estimating the potential exposure" without having to update this assessment, RDWA at 124, is indeed applicable as the use profile assumptions used in the assessment do not reflect realistic product use. Such refinements would 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. *See* DAS Comments on 2016 RHHRA at 73–77. Indeed, DAS presented a Preliminary Refined Drinking Water Assessment (MRID 50016001), a next-tier highly refined assessment, to the Agency in February 2016, which the Agency has not yet finished reviewing.

In sum, DAS is hopeful that the Agency will work on these critical drinking water issues during registration review and will consider refinements that DAS has previously provided to the Agency in preparing its final decision.

F. The Petition Does Not Shift the Burden to EPA to Again Prove that Chlorpyrifos is Safe.

The Objections repeatedly and wrongly assert that EPA has the burden to make a new safety determination in response to a petition to revoke tolerances. Petitioners' Objections at 32; States' Objections at 9.

Under Section 408 of the FFDCA, as amended by the FQPA, "[t]he Administrator may establish or leave in effect a tolerance for a pesticide chemical residue in or on a food only if the Administrator determines that the tolerance is safe. The Administrator shall modify or revoke a

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tolerance if the Administrator determines it is not safe." FFDCA § 408(b)(2)(A)(i), 21 U.S.C. § 346a(b)(2)(A)(i). "Safe" is defined by the FFDCA as meaning 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). In determining whether to revoke a tolerance, EPA must 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). Contrary to Petitioners' assertion, there is nothing in either FFDCA or FQPA suggesting that the burden is on the Agency or the registrant to make a new safety determination in response to a petition to revoke tolerances.

Under the FFDCA, "[a]ny person may file with the Administrator a petition proposing the issuance of a regulation . . . establishing, modifying, or revoking a tolerance for a pesticide chemical residue in or on a food." FFDCA § 408(d)(1), 21 U.S.C. § 346a(d)(1). After giving "due consideration" to the petition, the Administrator must either issue a final regulation establishing, modifying, or revoking a tolerance, issue a proposed regulation, or issue an order denying the petition. *Id.* § 346a(d)(4). Nowhere does the statute indicate that the petition cannot be denied unless and until EPA affirmatively makes a new "safety" determination under the FFDCA.

Indeed, the FFDCA's implementing regulations place the burden squarely on the *petitioner* to prove that the pesticide is not safe:

> The petition shall furnish reasonable grounds for the action sought. Reasonable grounds shall include an explanation showing wherein the person has a substantial interest in such tolerance or exemption from tolerance and an assertion of facts (supported by data if available) showing that . . . new data are available as to toxicity of the chemical, or that experience with the application of the tolerance or exemption from tolerance may justify its modification or revocation.

40 C.F.R. § 180.32(b). EPA's Order is consistent with these standards and with the Agency's prior responses to PAN/NRDC regarding the petition. *See, e.g.,* 2012 Bradbury Letter at 18 ("To show a lack of safety, petitioners would have to present a factual analysis demonstrating that . . . the [cumulative risk assessment] for chlorpyrifos poses unsafe cumulative exposures to the OP

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pesticides. Petitioners have not made such a showing. For this reason . . . EPA intends to deny the petitioners' request . . . .").

When the petition is denied, petitioners must submit objections to EPA, to which EPA must respond, *before* petitioners may obtain judicial review of the merits of EPA's Petition denial. *See* 21 U.S.C. § 346a(g)(2)(C) (Administrator must issue an order stating the action taken on each objection) *Id.* § 346a(h)(1) (order denying objections issued under § 346a(g)(2)(C) is reviewable in the court of appeals); *see also* 40 C.F.R. § 180.30(b) (review of an order denying a petition "shall not be the subject of judicial review under any other provision of law," and "judicial review is not available *unless an adversely affected party exhausts the[ ] objection procedures*, and any petition procedures preliminary thereto") (emphasis added). Thus, there is nothing in the FFDCA or its implementing regulations that places the burden on the Agency or the registrant to prove safety in response to a petition.

The only case cited by Petitioners in support of their burden-shifting argument, *Environmental Defense Fund, Inc. v. U.S. Department of Health, Education & Welfare*, 428 F.2d 1083 (D.C. Cir. 1970), a case not involving EPA, is readily distinguishable. There, petitioners challenged the Secretary of Health, Education and Welfare's refusal to publish their petition to establish a "zero tolerance" for DDT residues (an alleged carcinogen) in or on raw agricultural commodities. *Id.* at 1086. The court held that the agency had the burden of proving the safety of the existing tolerances for DDT, the pesticide at issue, *in light of findings by a government commission that "the evidence for the carcinogenicity of DDT in experimental animals is impressive."* *Id.* at 1085 (emphasis added). The court stated, in a footnote, that "[o]nce new evidence bearing on the safety of pesticide residues has been adduced or cited sufficient to justify reopening the issue of the validity of existing tolerances, as in the present case, the burden of establishing the safety of any tolerance remains on those who seek to permit a residue." *Id.* at 1092 n.27. The court relied on a provision of the FFDCA that is not in the current version of the statute, namely "that the procedures for amending or repealing tolerances should be the same as those for establishing tolerances." *Id.* (citing 21 U.S.C. § 346a(m)). The cited provision states that "[t]he Administrator shall prescribe by regulations the procedure by which regulations [establishing tolerances] under this section may be amended or repealed, and such procedure shall conform to the procedure provided in this section for the promulgation of regulations

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establishing tolerances." 21 U.S.C. § 346a(m). That provision was repealed in 1996 and replaced with 21 U.S.C. §§ 346a(d) and (e). H.R. Rep., pt. 1, 104th Cong. 2d Sess. 669 (1996). There is nothing in the current version of the FFDCA suggesting that the procedures for revoking tolerances should be the same as for establishing tolerances.

Petitioners' interpretation of the Agency's obligations in the face of a petition would lead to the unprecedented result that EPA is required to renew its safety finding each and every time a petition is filed, irrespective of the strength and quality of the evidence cited in support of the petition, and regardless of whether EPA is engaged in an ongoing scientific review of issues addressed in the petition through Registration Review. This is neither a logical nor workable interpretation of FFDCA's requirements, and there is nothing to indicate that Congress intended such a result.

In addition, unlike in *Environmental Defense Fund,* the unreliable and invalid epidemiology studies at issue here are far from "sufficient to justify reopening the issue of the validity of existing tolerances." Indeed, as discussed in detail above, neither EPA nor any of the SAP meetings convened to review the epidemiology studies found the studies to be conclusive or causal. In further contrast to *Environmental Defense Fund,* where petitioners were challenging the Secretary of Health, Education and Welfare's *refusal* to publish a petition, the Petition here underwent extensive public comment, and the Agency subsequently found that petitioners had failed to provide sufficient evidence that chlorpyrifos was not safe at existing tolerance levels. And, as EPA indicated in its denial of the Petition, its science-based review of chlorpyrifos will continue during registration review. This fact also clearly distinguishes the current matter from *Environmental Defense Fund.*

In sum, EPA made a safety determination in 2006, and that determination still remains in effect. The burden is on the petitioners seeking revocation of chlorpyrifos tolerances to demonstrate that the current regulatory standard for chlorpyrifos is not safe.

IX. CONCLUSION

For the foregoing reasons, EPA's March 29th, 2017 Order correctly denied the Petition because there is an extensive and complete set of animal toxicology data that support the current regulatory standard for chlorpyrifos, and the epidemiological and other studies advocated by

Petitioners are not reliable enough for regulatory decision-making. The Agency should therefore deny all of the Objections submitted in response to EPA's Order.

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Appendix A: Analysis of Additional Animal Toxicology Studies

Appendix A to Dow AgroSciences LLC's Response to Objections to EPA's Denial of Petition to Revoke All Tolerances and Cancel All Registrations for Chlorpyrifos: Analysis of Additional Animal Toxicology Studies

In recent years, Petitioners and others have claimed that there is a growing body of human epidemiology and experimental animal evidence showing associations between exposure to chlorpyrifos at levels below EPA's current regulatory standard and neurodevelopmental outcomes. However, as repeatedly demonstrated in Dow AgroSciences LLC's ("DAS's") prior and current comments, the epidemiology studies cited in support of these claims suffer from significant scientific limitations, precluding their use in regulatory decision-making. The same result applies to the experimental animal studies. Indeed, in 2012, EPA convened a Scientific Advisory Panel ("SAP") to address experimental animal studies involving chlorpyrifos, and the Panel found that the studies had significant limitations. EPA itself examined the animal literature with respect to chlorpyrifos in 2014, and again in 2016 with respect to organophosphates ("OPs") generally, and similarly identified weaknesses in the scientific research, further undermining claims of adverse effects at levels below the current regulatory standard.

This Appendix summarizes the SAP and EPA's critiques of animal toxicology studies examining (1) possible modes of action/adverse outcome pathways other than the well-established mode of action of cholinesterase inhibition, and (2) potential associations between chlorpyrifos exposure and neurodevelopmental outcomes. This Appendix then addresses additional animal toxicology studies not addressed in DAS's prior comments submitted to the Agency, including studies recently reviewed by the California Department of Pesticide Regulation, that alleged adverse neurodevelopmental outcomes. As demonstrated herein, these additional studies suffer from many of the same deficiencies and weaknesses noted by EPA and the SAP in their review of the animal literature, and do not support a claim that there is evidence supporting a departure from the current regulatory endpoint for chlorpyrifos.

A. EPA and SAP Criticisms of the Experimental Toxicology Research Regarding Chlorpyrifos

In 2012, EPA convened an SAP to evaluate the scientific research associating chlorpyrifos with neurodevelopmental and neurobehavioral outcomes. In its Issue Paper

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provided to the 2012 SAP, EPA identified a number of limitations in the animal toxicology studies examining non-cholinergic modes of action:

- [T]here are several lines of evidence for actions of chlorpyrifos distinct from the classical mode of action of cholinesterase inhibition . . . however, . . .most of these studies have not been designed with the specific goal of construction or testing an adverse outcome pathway. *Thus, there are not sufficient data available to test rigorously the causal relationship between effects of chlorpyrifos at the different levels of biological organization in the nervous system.* EPA, Meeting of the FIFRA Scientific Advisory Panel, Draft Issue Paper: Scientific Issues Concerning Health Effects of Chlorpyrifos (2012) ("EPA 2012 Issue Paper") at 35 (emphasis added).

- Because many of these papers report a number of positive as well as negative findings, *the Agency had previously taken the approach of comparing responses that were observed following various exposures to a common dose,* 1 mg/kg/d (FIFRA Scientific Advisory Panel (SAP), 2008a; [USEPA], 2011). A more robust approach is taken here, to include important factors such as dose-response and differences in exposure scenarios. . . . *unfortunately, many of the chlorpyrifos studies have evaluated only one dose. Id.* at 39 (emphasis added).

- All testing reported herein was conducted after weaning, and there is a presumption that the effects are permanent; however, no study has directly addressed this issue, and there is a range in test ages. *Dose-response is not always evident, since many studies only use one dose*, and of those using two or more doses, there is not always a monotonic response. Furthermore, the summary presented herein combines studies of different dosing regimens. *Id.* at 52 (emphasis added).

- 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. *Id.* (emphasis added).

- 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; thus far, only one study (Braquenier, et al., 2010) has tested a dose lower than the point of departure.* The broad profile of neurological effects that have been reported do not aid in the development of a specific AOP, and as described in section 3.2.1., existing experimental studies have not been designed to examine and track possible mechanisms from early initiating events to the final neurological outcome. Such studies represent longer term research efforts by the different laboratories." *Id.* at 52–53 (emphasis added).

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EPA sought the SAP's guidance on these and other issues. Following its review of the animal toxicology research, the SAP similarly found the evidence insufficient to establish a plausible mode of action/adverse outcome pathway linking chlorpyrifos exposure with adverse outcomes:

> Question 2.1
> As discussed in Section 3.2.1, although there are numerous mechanistic studies in the scientific literature, the research on different hypotheses does not provide sufficient data to establish causal linkages among different levels of biological organization to show how effects lead to adversity. As such, a mode of action or adverse outcome pathway leading to effects on the developing brain cannot be established at this time. Moreover, although multiple biologically plausible hypotheses are being pursued by researchers, based on the current state of the science, no one pathway has sufficient data to be considered more credible than the others. *Please comment on the Agency's preliminary conclusion that although there are multiple biologically plausible hypotheses being evaluated by research scientists, the mechanistic experimental toxicology data do not yet support a coherent set of key events in a mode of action/adverse outcome pathway.*
>
> The Panel agrees with the Agency's conclusion that based on the current state of the science, no one pathway has sufficient data to be considered more credible than the others with respect to a causal link between chlorpyrifos exposure and neurodevelopmental outcome.

EPA, Transmittal of Meeting Minutes of the FIFRA Scientific Advisory Panel Meeting held April 10-12, 2012 on "Chlorpyrifos Health Effects" at 13 (July 11, 2012) ("2012 SAP Minutes").

The 2012 SAP noted limitations in the designs of many of the experimental studies and expressed concern with the use of the dimethyl sulfoxide (DMSO) as a vehicle:

> [S]tudies evaluating neurodevelopmental effects entailed experimental designs that do not permit an efficient means of determining a point of departure for chlorpyrifos. . . . ***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. at 12 (emphasis added). The 2012 SAP also found that there were "no studies . . . identified that showed effects on behavior at low levels of AChE inhibition, including at 1.0 mg/kg of chlorpyrifos" and that "*[d]oses below 1.0 mg/kg/day chlorpyrifos did not show convincing evidence of neurobehavioral effect; hence, no extrapolation to lower doses in terms of AChE inhibition is possible* from the data reviewed herein." *Id.* at 39 (emphasis added).

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Ultimately, the 2012 SAP expressed confidence in the current regulatory standard for chlorpyrifos, stating that, "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." *Id.* at 12.

B. EPA Has Been Critical of Experimental Toxicology Research Purporting to Link OP/Chlorpyrifos Exposure with Adverse Neurodevelopmental Effects

EPA's more recent reviews of the experimental toxicology research have echoed the 2012 SAP's conclusions. As demonstrated below, EPA's 2014 and 2016 literature reviews demonstrate that EPA places low confidence in animal toxicology studies reported since 2008 regarding neurodevelopmental effects associated with chlorpyrifos exposure, certainly at exposure below the threshold for 10% red blood cell cholinesterase inhibition ("RBC ChEI").[1]

For example, in the December 29, 2014 Revised Human Health Risk Assessment for Chlorpyrifos ("2014 RHHRA"), EPA expressed confidence in AChE as a health-protective endpoint:

> Since the MOA(s)/AOP(s) is/are not established for neurodevelopmental outcomes . . . it is not possible to describe the concordance in key events or biological steps leading to neurodevelopmental outcomes. As such, the quantitative linkages between MIEs, intermediate steps, and ultimately the adverse outcome (i.e., neurodevelopmental effects) cannot be determined. Experimental toxicology studies in rodents suggest that long-term effects from chlorpyrifos exposure may occur. Due to the dose selections in most of these *in vivo* studies evaluating effects such as behavior and cognition, *it is not known whether such adverse effects would be shown at doses lower than those which elicit 10% RBC AChE inhibition.* It is notable, however, that comparing the lowest NOAEL observed in the *in vivo* animal studies (0.2 mg/kg/day; Billauer-Haimovitch et al., 2009) for the neurodevelopmental outcomes to the repeated dosing reliable $BMDL_{10}$ ranging from 0.05-0.17 mg/kg/day for RBC AChE inhibition suggests that AChE inhibition is a sensitive endpoint.

2014 RHHRA at 44–45 (emphasis added).

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[1] As set forth in Dow AgroSciences LLC's Response to Objections, acetylcholinesterase ("AChE") inhibition ("ChEI") is the mode/mechanism of action for effects to the mammalian system with respect to chlorpyrifos. 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"). RBC ChEI 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.

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In its 2014 RHHRA, EPA reviewed six animal toxicology studies published since the 2012 SAP. EPA concluded that the study findings were inconsistent with prior research showing no effects, and studies that reported adverse effects employed doses that exceeded those known to cause cholinesterase inhibition:

> For half of the studies, the lowest dose was 1 mg/kg/d, and two studies used the oxon, making it difficult to compare dose levels. Only one study used a lower dose, 0.36 mg/kg/d, in feed, and even this level was sufficient to produce a great degree of RBC ChE inhibition. . . .
>
> *Conclusions: 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.*

Id. at 196–97 (emphasis added).

EPA also found that newer lines of research were not sufficient to establish a biologically plausible mode of action/adverse outcome pathway:

> With respect to modes of action/adverse outcome pathways leading to neurodevelopmental effects, *at the present time, there is no established series of causal key events at a biological level of organization relevant to the risk assessment (i.e., adverse neurodevelopmental effects from gestational and/or postnatal exposure)*. . . . Some of the new studies since 2012 have been integrated in this section. *Despite the newest studies, the agency does not believe that any of the current lines of research support a coherent set of key events and that much work remains to elucidate the modes of action and adverse outcome pathways of chlorpyrifos toxicity.*

Id. App. 1, p. 144 (emphasis added).

In its December 29, 2016 Updated Literature Review on Neurodevelopment Effects & FQPA Safety Factor Determination for the Organophosphate Pesticides (the "2016 Literature Review"), EPA conducted a review of the scientific literature examining links between exposure to organophosphate pesticides ("OPs") with neurodevelopmental outcomes. EPA summarized several of the key 2012 SAP and 2014 RHHRA findings as follows:

> A review of the scientific literature on potential MOA/AOP leading to effects on the developing brain was conducted for the 2012 FIFRA SAP meeting . . . and updated for the [2014 RHHRA]. In short, multiple biologically plausible hypotheses and pathways are being pursued by researchers including: AChE as a morphogen; cholinergic system; endocannabinoid system; reactive oxygen species; serotonergic system; tubulin, microtubule associated proteins and axonal transport.

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> However, no one pathway has sufficient data to be considered more plausible than the others. . . . The SAP concurred with the agency in 2008 and 2012 about the lack of definable key events in a MOA/AOP leading to developmental neurobehavioral effects.

Id. at 7. EPA noted that "[s]ince the 2014 [RHHRA], *there have been no substantive changes in the ability to define and quantify steps in an MOA/AOP leading from exposure to effects on the developing brain.*" *Id.* (emphasis added).

While the 2016 Literature Review specifically focused on OPs other than chlorpyrifos, some of the agency's conclusions are consistent with conclusions reached for chlorpyrifos, relative to studies investigating potential neurodevelopmental effects. For example, EPA concluded:

> Overall, in the studies for which there are direct or comparable data, it is clear that the dosing paradigms produced AChE inhibition and in some cases maternal toxicity. Indeed, there are no studies reporting or even suggesting a lack of AChE inhibition in the dam and/or fetus/pup at any time during dosing. Thus, it is not known whether exposure paradigms that do not inhibit AChE would produce any neurobehavioral effects.

Id. at 23. As discussed below, this conclusion is important because it confirms that animal toxicology studies using doses at or above those known to cause cholinesterase inhibition do not justify a departure from the current point of departure.

In addition, in Section 2.1.5 of the 2016 Literature Review, Conclusions on In Vivo Laboratory Animal Studies, EPA stated:

> For chlorpyrifos, there are >30 papers on developmental neurotoxicity; for the remaining OPs, the literature is sparse with very few studies for each OP.... The studies span over decades, and many of the lower quality studies were the earlier ones; however, some very recent papers also have significant deficits. Methodological detail is lacking, inappropriate statistical analyses are applied, results are cursorily described and /or inaccurately presented, and interpretation of some behavioral changes is faulty. Overall, most studies have significant shortcomings and/or are of low quality.
>
> The most commonly tested behaviors considered aspects of cognition. In the majority of studies, some sort of cognitive deficit was detected, especially with working memory performance (radial arm maze) and conditioned response retention (passive avoidance). However, in many cases there was no dose-response, there was some gender specificity which did not replicate in multiple studies, and cognitive improvement instead of deficit was noted in a few papers. Changes in motor activity in offspring were generally not reported, and the direction of change differed in the papers reporting such effects. There is generally not enough

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> information to make definitive statements about OP effects on other types of neurological disorders.

Id. at 24–25. While these statements refer to studies involving OPs other than chlorpyrifos, the same observations and criticisms apply to the literature on chlorpyrifos and putative neurodevelopmental toxicity. These statements also show that the Agency recognizes the importance of scientific study design and conduct and of sound interpretation and reporting of observed effects.

EPA also recognized in the 2016 Literature Review the importance of considering cholinesterase inhibition in studies assessing potential neurodevelopmental toxicity, observing that:

> Few published papers included AChE measurements of the dams and/or offspring, but where measured, all doses used inhibited AChE to some degree. . . . Since there are no studies with low doses that definitively do not inhibit AChE, there is no information in the animal literature that shows whether or not there would be developmentally neurotoxic outcomes at those lower exposures.

Id. at 25.

In its overall conclusion of the 2016 Literature Review, EPA stated:

> Overall, a definitive mode of action or adverse outcome pathway leading to effects on the developing brain cannot yet be established because of insufficient data establishing the causal linkages among different levels of biological organization to adversity. For example, while there is *in vitro* evidence relating binding of chlorpyrifos or the chlorpyrifos oxon to AChE and the subsequent decrease in neurite outgrowth at the cellular level, the relationship between neurite outgrowth and neurodevelopmental consequences has not been established. As described in the NRC report "Toxicity Testing in the 21st Century". . . , to develop an adverse outcome pathway not only is it necessary to establish plausible relationships among the key events, but quantitative relationships also need to be established.

Id. at 175.

The above summary of EPA's most recent analysis on OPs and potential neurodevelopmental toxicity as reported in the open scientific literature is relevant to a review of the literature specific to chlorpyrifos. Many of EPA's criticisms of the scientific literature claiming links between OP exposure and adverse neurodevelopmental outcomes apply with equal force to the scientific literature for chlorpyrifos, further demonstrating that there is no scientific basis for proposing a point of departure for chlorpyrifos other than cholinesterase inhibition. There is simply not sufficient and replicated scientific evidence, nor a plausible and

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proven MOA/AOP, connecting exposure to chlorpyrifos at levels below the current regulatory standard with adverse neurodevelopmental outcomes.

C. Recent Experimental Toxicology Studies Reviewed by EPA Do Not Support Adverse Effects for Chlorpyrifos at Levels Below the Current Regulatory Standard

In recent years, DAS has reviewed and commented publicly on many of the same experimental toxicology studies and literature examined by EPA in its 2014 and 2016 reviews and advanced by Petitioners and others as showing adverse neurodevelopmental effects at levels below the current regulatory standard.[2] As detailed in DAS's prior comments, there is no compelling or consistent animal toxicology evidence to support the contention that neurodevelopmental outcomes occur at exposures below 10% RBC ChEI. In virtually all of these studies, the lowest dose employed was at or above levels known to result in 10% RBC ChEI, cholinesterase inhibition was not measured at all, findings were inconsistent, and/or there were design flaws and methodological confounders undermining the validity of the study's findings.

Several additional studies referenced in EPA's 2016 Literature Review but for which DAS has not previously submitted specific comments are summarized in Table 1, below. These studies are very similar to literature evaluating potential effects and numerous endpoints relative to chlorpyrifos exposure in *in vitro* and *in vivo* test systems. A collective analysis of the eleven studies in Table 1 reveals that they suffer from many of the same deficiencies and limitations EPA identified in its 2014 and 2016 reviews and in DAS's prior comments of studies of similar nature and design.

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[2] *See, e.g.,* Dow AgroSciences LLC's Response to EPA's [RHHRA] for Chlorpyrifos Registration Review, EPA Dkt. EPA-HQ-OPP-2008-0850-0845, at 57–64 (Apr. 2015); Dow AgroSciences LLC's Comments on 2016 [NODA/RHHRA] and Refined Drinking Water Assessment for Chlorpyrifos, EPA Dkt. EPA-HQ-OPP-2015-0653-0651, at 33 and Appendix D (Jan. 2017); Dow AgroSciences LLC's Amicus Brief in Support of EPA, *League of United Latin Am. Citizens, et al. v. Wheeler*, No. 17-71636, ECF No. 72-2, at 20–23 (9th Cir. Mar. 15, 2018).

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Table 1. Summary of Investigative Studies Associating Chlorpyrifos Exposure with Neurodevelopmental Outcomes

Citation	Test System	General Focus	Dose(s)	Exposure Route	Exposure Duration	Vehicle	Dose-Response	ChEI Measured	NOEL Defined
Ridano et al. 2017	In vitro	Placenta as target of toxicity	10, 50, 100 uM	N/A	N/A	DMSO	Yes/No	No	Yes/No
Icenogle et al. 2004	Rat	Behavioral effects	1, 5 mkd	SC inj.	GD 9-12	DMSO	Yes/No	No	Yes/No
Billauer-Haimovitch et al. 2009	Mouse	Visuospatial effects	1, 3, 5, 10, 20 mkd	SC inj.	GD 9-18	DMSO	Yes/No	No	Yes/No
Turgeman et al. 2011	Mouse	Neurobehavioral effects	3 mkd	SC inj.	GD 9-18	DMSO	No	No	No
Braquenier et al. 2010	Mouse	Anxiety effects	0.2, 1, 5 mkd	Oral gavage	GD15-PND14	Corn oil	No	Yes – brain only at 5 mkd	Yes – 0.2 mkd
Venerosi et al. 2010	Mouse	Anxiety effects, aggressive behavior	6 mkd	Oral gavage	GD 14-17	Peanut oil	No	No	No
Levin et al. 2001	Rat	Learning and memory effects	1 mkd 5 mkd	SC inj.	PND1-4 PND 11-14	DMSO	No	No	No
Vatanparas et al. 2013	Rat	Passive avoidance performance	1 mkd	SC inj.	GD15-18 PND1-4	DMSO	No	No	No
Mamczarz et al. 2016	Guinea Pig	Spatial learning	25 mkd	SC inj.	GD 53-63	Peanut oil	No	Yes – RBC ChEI at 25 mkd	No
Slotkin et al. 2015	Rat	Expression of serotonin receptors	1 mkd	SC inj.	PND 1-4	DMSO	No	No	No
Venerosi et al. 2008	Mouse	Social behavior effects	3 mkd	SC inj.	PND 11-14	Peanut oil	No	No	No

Specifically, there are various test systems employed in these studies (*in vitro*, *in vivo* studies using different animal species), different endpoints or outcomes of interest, and often inconsistent results within and across studies. Taken together, these issues preclude drawing reliable conclusions on the ability of chlorpyrifos to elicit neurodevelopmental effects, certainly

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not below the current regulatory point of departure (10% RBC ChEI). Among these eleven studies, only one used a dose level below 1 mg/kg/day (Braquenier et al. 2010; 0.2 mg/kg/day) and this was a NOEL in this study with 1 mg/kg/day representing a LOEL. Moreover, many studies employed only a single dose (exposure scenario) and only two used three or more doses, which is the standard for discerning whether a true dose-response relationship exists.

In addition, many of the studies used subcutaneous injection as the route of exposure, which is not relevant to human exposure scenarios. A number of the studies also used the known neurotoxicant DMSO as the vehicle. Because DMSO has neurotoxic properties of its own, its use in experimental studies that specifically are addressing neurodevelopmental outcomes is a significant confounder and challenge relative to study result interpretation. As noted above, the use of DMSO as a vehicle has been the subject of criticism by multiple scientific and regulatory entities, including the FIFRA SAP.

Finally, and perhaps most importantly, cholinesterase inhibition, specifically RBC inhibition, was measured in only one study, Mamczarz et al. 2016, which employed a very high dose (compared to other experimental studies and to human exposure scenarios). The failure of investigators in the other studies to concomitantly measure and quantify the degree of RBC cholinesterase inhibition precludes a conclusion that there are neurodevelopmental effects below the lowest dose employed, and certainly below the threshold of 10% RBC ChEI (a dose level which is far below those used in any of these eleven studies above).[3]

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[3] All of these studies stand in stark contrast with the results of the EPA-required Marty et al. 2012 study. There, 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 show 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. In addition, while there is a misperception that 1 mg/kg/day is the threshold for cholinesterase inhibition, the Marty et al. study (2012) clearly demonstrates following repeated dosing in young and adult rats that 1 mg/kg/day is associated with in excess of 70% RBC ChEI in adults, and in excess of 60% and 40% RBC ChEI in male and female pups, respectively. This study confirms

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D. Recent Experimental Toxicology Studies Cited by the California Department of Pesticide Regulation Do Not Support Adverse Effects for Chlorpyrifos at Levels Below the Current Regulatory Standard

The California Department of Pesticide Regulation ("DPR") has reviewed additional studies, during its deliberations over the listing of chlorpyrifos as a Toxic Air Contaminant ("TAC"). Specifically, DPR has reviewed five studies, summarized in Table 2, below, allegedly supporting its contention that neurodevelopmental outcomes in experimental animals following exposure to chlorpyrifos occur below the threshold for cholinesterase inhibition.

Table 2. Summary of Recent Studies Cited by CA DPR as Indicative of Neurodevelopmental Effects Associated with Chlorpyrifos Exposure Below the Threshold for Cholinesterase Inhibition

Citation	Test System	General Focus	Dose(s)	Exposure Route	Exposure Duration	Vehicle	Brain ChEI	RBC ChEI	Notes
Carr et al., 2017	Rat	Anxiety behavior	0.5, 0.75, 1.0 mkd	Oral gavage	PND10-17	Corn oil	19% decrease at 1 mkd	Not measured	No effects on brain ChEI at lower doses; reported decreased anxiety – opposite of Silva et al.
Lee et al., 2015	Mouse	Adult behavior and cognitive impairment	0.1, 1.0, 5.0 mkd	Oral gavage	PND10	Egg lecithin/ peanut oil emulsion	No significant brain ChEI	Not measured	Results questionable as 5 mkd should cause brain ChEI
Gomez-Gimenez et al. 2017a	Rat	Motor activity and coordination	0.1, 0.3, 1.0 mkd	Oral gavage	GD7-PND21	Corn oil – given in sweet jelly	Not measured	Not measured	
Gomez-Gimenez et al. 2017b	Rat	Spatial learning	0.1, 0.3, 1.0 mkd	Oral gavage	GD7-PND21	Corn oil – given in sweet jelly	Not measured	Not measured	
Silva et al., 2017	Rat	Anxiety behavior	0.01, 0.1, 1.0, 10.0 mkd	Oral gavage	GD14-20	9% saline with Tween 20	Not measured	Not measured	Reported increased anxiety – opposite of Carr et al

the protective and conservative nature of using 10% RBC ChEI as a point of departure for risk assessment purposes.

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These studies, suffer from the same flaws and limitations as the eleven studies summarized in Table 1. Only two studies measured brain cholinesterase activity, with only one of them (Carr et al., 2017) reporting modest ChEI at the highest dose (1 mkd). Notably, *none* of the studies measured RBC cholinesterase inhibition, the current point of departure used by EPA and other global authorities as the conservative endpoint upon which to base permissible exposure levels to humans.

Because Silva et al. (2017) used the lowest dose (0.01 mg/kg/day) of any of the studies, this study in particular warrants comment as DPR has claimed that "the most important implication of this study is that the threshold for CPF-induced neurobehavioral effects in young rats following gestational exposure may be as much as 10-fold lower than the reported threshold of 1 mg/kg/day established for RBC AChE inhibition in adult rats." DPR, Draft Evaluation of Chlorpyrifos as a Toxic Air Contaminant: Risk Characterization of Spray Drift, Dietary, and Aggregate Exposures to Residential Bystanders, at 57 (Dec. 2017). But, this statement is factually incorrect, as there is clear evidence that the threshold for RBC AChE is well below 1 mg/kg/day (Marty et al., 2012 and footnote included above).

A closer review of Silva et al. (2017) reveals that this study reported on anxiety-like behavior in rat offspring following exposure to chlorpyrifos during pregnancy (i.e., GD14-20). They employed doses ranging from 0.01 to 10 mg/kg/day, but failed to report on purity of the test material and did not measure cholinesterase inhibition of any type. The group size ranged from eleven to fourteen pregnant females per group. The actual number of offspring tested for behavioral effects on PND 21 and PND 70 is not stated. It is not clear whether testing included littermates and, if so, how the study controlled for the presence of littermates. Silva et al. (2017) reported effects at 0.1-1.0, citing axiogenic-like, but not depressive-like behavior at PND21 (without causing fetal toxicity), but the effect was reversed by PND 70. This begs the question whether increased or decreased anxiety-like behavior is biologically significant and whether both are adverse, or whether one is adverse while the other is not, particularly as other investigators have reported decreased anxiety related to chlorpyrifos exposure (Carr et al., 2017). There was no dose-response for this reported effect among the top three dose levels; while locomotor activity was reported as statistically significant, the increased (relative to control) motor activity at 0.1 mg/kg/day was virtually the same as that reported following exposure to 10 mg/kg/day.

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While the inferred NOEL for this study would be 0.01 mg/kg/day, the absence of a defined dose-response at the top three dose levels calls into question whether this reported effect is treatment-related at all.

In short, a review of these additional five studies reveals that, as with the eleven studies summarized in Table 1, it cannot be claimed that neurodevelopmental outcomes in animals occurr below the threshold for ChEI, as virtually no study to date has included measurements of RBC ChEI. Moreover, as discussed above, Marty et al. (2012) demonstrates that this threshold is well below 1 mg/kg/day.

E. Conclusion

Chlorpyrifos continues to be investigated in experimental settings relative to claims that it is associated with neurodevelopmental outcomes and that *in vitro* and *in vivo* animal studies are supportive of epidemiology studies alleging links between chlorpyrifos exposure below the current regulatory standard and reduced IQ, loss of working memory, attention deficit disorders, and delayed motor development in young children. This expansive body of animal literature has been evaluated for over ten years by the EPA and its FIFRA SAP, as well as international regulatory bodies. To date, a plausible and biologically meaningful/replicated mode of action explaining how chlorpyrifos could be exerting effects on neurodevelopment at dose levels below the current regulatory endpoint, in either animals or humans, has not been identified. This has been confirmed by EPA and the SAP. In fact, very few studies, despite claims to the contrary, have employed sufficiently low dose levels (below 1 mg/kg/day), particularly those below the threshold for RBC cholinesterase inhibition, to even probe this hypothesis. Moreover, the vast majority of studies, including the sixteen (eleven in Table 1; five in Table 2) reviewed above, have multiple confounding variables and experimental challenges which preclude their use for regulatory decision-making. There is simply no credible support for the statement that there are multiple studies indicative of neurodevelopmental effects caused by exposure to chlorpyrifos below the threshold for cholinesterase inhibition. Global regulatory authorities have utilized inhibition of cholinesterase inhibition, specifically RBC cholinesterase inhibition, as the conservative and protective point of departure which protects against all other putative toxicities. There is no scientific basis to change this conclusion.

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Appendix B: A Commentary on Some Epidemiology Data for Chlorpyrifos by Toxicology Excellence for Risk Assessment

Title

New Analysis of Data from Columbia Study Publication (Rauh et al. 2011) Demonstrates Need for Raw Data to be Made Available and Raises Additional Questions about the Scientific Validity of Alleged Link Between Exposures to Chlorpyrifos and Neurodevelopmental Effects

Data Requirements

N/A

Authors

GR Oliver[1] and DR Juberg[2]

Study Completed Date

July 9, 2018

Performing Laboratory

Dow AgroSciences, LLC
9330 Zionsville Rd
Indianapolis, IN 46268

Study ID: GRO-072018

STATEMENT OF NO DATA CONFIDENTIALITY CLAIMS

Compound: Chlorpyrifos

Study Title: New Analysis of Data from Columbia Study Publication (Rauh et al. 2011) Demonstrates Need for Raw Data to be Made Available and Raises Additional Questions about the Scientific Validity of Alleged Link Between Exposures to Chlorpyrifos and Neurodevelopmental Effects

No claim of confidentiality, on any basis whatsoever, is made for any information contained in this document. I acknowledge that information not designated as within the scope of FIFRA sec. 10(d)(1)(A), (B), or (C) and which pertains to a registered or previously registered pesticide is not entitled to confidential treatment and may be released to the public, subject to the provisions regarding disclosure to multinational entities under FIFRA sec. 10(g).

Company: Dow AgroSciences LLC

Company Agent: George Oliver

Title: Regulatory Leader

Signature: George Oliver

Date: July 9, 2014

THIS DATA MAY BE CONSIDERED CONFIDENTIAL IN COUNTRIES OUTSIDE THE UNITED STATES

STATEMENT OF COMPLIANCE WITH GOOD LABORATORY PRACTICE STANDARDS

Compound: Chlorpyrifos

Title: New Analysis of Data from Columbia Study Publication (Rauh et al. 2011) Demonstrates Need for Raw Data to be Made Available and Raises Additional Questions about the Scientific Validity of Alleged Link Between Exposures to Chlorpyrifos and Neurodevelopmental Effects

The study described in this report was conducted in accordance with the following Good Laboratory Practice Standard:

United States Environmental Protection Agency
Title 40 Code of Federal Regulations Part 160
Federal Register, 17 August 1989

Organization for Economic Co-Operation and Development
ENV/MC/CHEM(98)17, Paris – January 26, 1998

All phases of this study were conducted according to the final rule of the FIFRA Good Laboratory Standards, 40 CFR 160.

George Oliver
Sponsor
Dow AgroSciences LLC

Date: July 9, 2018

George Oliver
Submitter
Dow AgroSciences LLC

Date: July 9, 2018

George Oliver
Study Director
Dow AgroSciences LLC

Date: July 9, 2018

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Summary

As part of its statutorily required Registration Review of the pesticide chlorpyrifos, EPA has been evaluating an epidemiology study conducted by researchers with the Columbia Center for Children's Environmental Health (CCCEH) (the "Columbia study"). The Columbia study, and the articles published under that study, claim an association between de minimis amounts of chlorpyrifos allegedly found almost twenty years ago in the umbilical cord blood of a cohort of mothers enrolled in the study and neurodevelopmental effects in their children later in life

EPA has previously proposed using the Columbia study as a primary basis for setting new regulatory endpoints for chlorpyrifos. The proposed use of the Columbia study for regulatory decision making has been challenged in public comments, independent reviews and even by EPA's FIFRA Scientific Advisory Panel (SAP). In light of the continuing concerns regarding the validity of the Columbia study, Dow AgroSciences (DAS) asked Toxicology Excellence for Risk Assessment ("TERA"), an independent nonprofit with a mission to protect public health, to examine certain aspects of the Columbia study. TERA looked at the alleged link between chlorpyrifos exposure and neurodevelopmental outcomes reported in one of the most cited publications from the Columbia study (Rauh et al. 2011), by analyzing the data that could be derived from the figures and text of the published article. TERA's methodology and findings are summarized in detail in the attached report

The TERA report's findings raise a number of serious scientific concerns about the reliability of the Columbia study's data and validity of the Columbia study's conclusions. Concerns similar to these have been expressed by prior SAPs and other experts. The TERA findings revealed that not all data were included in the Rauh et al. (2011) analyses. Any exclusion or missing data could impact the conclusions. The TERA report's findings underscore the critical importance of obtaining and analyzing the underlying raw data in order to assess the replicability of the Columbia study's claims. In addition, the TERA report notes that use of different, but generally accepted, graphical representations or plots of the data impacted the trends observed and therefore the conclusions drawn. The impact of simple replotting of the data raises further

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questions about the scientific validity and strength of conclusions drawn in the Rauh et al. (2011) publication and the Columbia study.

The TERA findings reported here regarding Rauh et al. (2011), along with challenges raised by other experts, show the findings cannot be considered reliable for purposes of any regulatory decision-making, including but not limited to establishing a new health-based regulatory endpoint or assigning additional or increasing Uncertainty or Safety Factors. EPA should continue to insist upon access to the full set of raw data. The TERA analysis relies on the limited data shared with the scientific community by Rauh et al. (2011). EPA access to and independent analysis of all the raw data would help to address and work towards resolution of the questions and concerns raised in this report. EPA is encouraged to share any progress on obtaining the full set of raw data and resolving these concerns.

US EPA's History of Proposed Uses of the Columbia Study

During 2015-2016, the Columbia study served as the foundation for EPA to propose a link between exposure to chlorpyrifos below the current regulatory standard and neurodevelopmental effects. In November 2015, EPA issued a proposed rule to revoke all tolerances previously established for food uses of chlorpyrifos (*Chlorpyrifos; Tolerance Revocations; Proposed Rule and EPA Analysis of the Small Business Impacts of Revoking Chlorpyrifos Food Tolerances*). Then, in 2016, EPA advanced another regulatory standard for chlorpyrifos (*Chlorpyrifos: Tolerance Revocations; Notice of Data Availability and Request for Comment*). Each time, the Columbia study was the centerpiece for EPA's new proposal. The EPA has given weight to this particular study since it measured chlorpyrifos, not the metabolite, in maternal and cord blood. But, DAS along with other external experts and including USDA have raised serious challenges to EPA's reliance on the Columbia study. Even EPA's own FIFRA Scientific Advisory Panel (SAP) in 2016 strongly criticized EPA's proposed use of this study to set a new regulatory endpoint. Concerns have been raised over the methodology of the study and scientific validity of the conclusions. A major criticism raised repeatedly has been that, 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.

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Claims also have been made that the findings reported by the Columbia study are supported by some toxicological studies and other epidemiology studies. However, the scientific validity of these cited toxicological studies has been repeatedly challenged (Oliver, et al. 2016). And, when looking across the epidemiology studies, the neurodevelopmental outcomes have been over-generalized. The specific results are not reproduced in the other studies, challenging any claim of a link between neurodevelopment effects and chlorpyrifos exposures. In fact, consideration of the findings *in total across* these studies does not support and even counters the claim that the epidemiology studies support the Columbia study (Burns and Oliver, 2018; Refer to Section IV of this report). With the validity of the results and conclusions claimed by the Columbia study already in question, TERA's analysis of data from the Rauh et al. (2011) publication casts further doubt on the scientific validity of the findings of the Columbia study.

The Columbia Study – Background on the study

The Columbia University researchers have been studying a group of New York City children born between 1998 and 2002. The investigators have followed certain aspects of the development of these inner-city children of African American and Dominican descent for approximately 15 years. The study started by looking at the many problems and environmental challenges existing in public housing such as holes in the ceiling, leaking pipes and unrepaired water damage, each reported by more than a third of the mothers, which in turn were associated with cockroach and rodent sightings. Measures of, "unmet needs" that included inadequate food, housing or clothing during pregnancy were counted. The investigators also evaluated the education, intelligence, and income of the mothers, which are predictors of childhood development. Unavailable was information about the father including paternal IQ. From the many publications from the Columbia study it is evident that this was a very disadvantaged group of children.

The Columbia study was designed to look at many environmental factors that may affect childhood health. To this end, the investigators tested the household air and infant cord blood for numerous different chemicals, elements (such as lead), and pesticides. The Columbia study researchers have multiple publications in the peer-reviewed literature on correlations between a few of these exposure estimates from birth and subsequent development during childhood, but have not yet reported on all.

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The Columbia study only reported statistical correlations, did not prove cause and effect, and failed to consider other plausible causes for their reported developmental outcomes

While the Columbia researchers attribute some correlations of lower test scores with higher chlorpyrifos levels, correlation alone does not prove a causal relationship. The long-standing and well-documented effect for chlorpyrifos used as the regulatory endpoint by regulatory agencies globally is cholinesterase inhibition. EPA is not able to find a biological explanation (i.e., mode of action), despite numerous attempts to identify one, demonstrating how chlorpyrifos in the body might affect neurodevelopment at levels below the current regulatory endpoint of cholinesterase. Extensive research outside the EPA in both humans and animals also shows there is no biological plausibility for the claim of a cause and effect relationship between the alleged low levels of exposure to chlorpyrifos and findings reported in the Columbia study. As discussed in the attached brief (Burns and Oliver, 2017; Refer to Section III of this report) there are multiple other plausible causes for the effects reported in the Columbia study. Most of these were either not considered or unmeasured in the Columbia study, but are important in understanding the underlying factors of childhood development. These alternate explanations need to be fully considered and accounted for when attempting to establish any cause-and-effect relationships.

Analysis of the Columbia study's publication by Rauh et al. (2011) raises serious challenges to the study's conclusion

One of the most cited publications from the Columbia study is Rauh et al. (2011), which claimed statistically significant associations for some reported neurological effects in infants with low levels of chlorpyrifos (CPF) allegedly detected in cord blood at the time of birth. Specifically, the publication reported findings of deficits in Working Memory Index and Full-Scale IQ of the children at 7 years old and alleged an association with prenatal exposure to chlorpyrifos. Although the underlying data have not been made available for validation, despite repeated requests from EPA, as discussed in the report by TERA, an analysis of the Figures in the publication enabled partial data extraction and analysis. The analysis of these extracted data raise significant questions about the conclusions put forward by Rauh et al. (2011).

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Missing data likely impacted findings and conclusions

The analysis by TERA revealed that data from 35% of 265 children described in the text of the publication by Rauh et al. (2011) were missing from one of the figures and 15% of the data were missing from another figure. Both figures were the basis in the publication for the claim of an alleged association with developmental effects. While some of the data which appear to be missing are possibly a result of overlay of data points not observable in these published figures, such overlay cannot reasonably be expected to account for the extent of missing data. Furthermore, as noted in the TERA report, in correspondence to the USEPA, Rauh et al. admit to selectivity of the data included in their analysis and publication (see Footnote 10 and Appendix A of TERA report). Specifically, data from the four children having the alleged highest levels of chlorpyrifos detected were removed from these figures because, according to Rauh et al. (2011) at least one data point "drastically impacts inference", which strongly suggests that the statistical significance of the findings might have changed if those data points had been included.

Plotting the data by different methods shows differing results, thereby challenging the strength and validity of claimed associations

TERA also demonstrates that a simple reanalysis/replotting of data from Rauh et al. (2011) significantly impacts the scale or direction of the effects trend reported. When the data for Full-Scale IQ are replotted in a different manner, consistent with a standard risk assessment approach, the evidence for an effect does not exist. And when the Working Memory Composite Scores are plotted differently, a reduced effect is found. As TERA points out, whether one method of plotting these data is superior to another can be debated, but if the reported association between claimed exposure levels and effects were scientifically strong, the resulting interpretations should not be affected by the method of plotting used

Conclusion

The new analysis of the data presented in Rauh et al. (2011) shows the reported associations between alleged chlorpyrifos levels in the mother's cord blood and Working Memory and Full

Scale IQ in their children have serious shortcomings and cannot be independently replicated. Potential impact of missing data, which appear not to have been included in the Rauh et al. (2011) figures, along with the demonstrated impact of replotting of the data using different approaches, raise serious questions about the conclusions of the paper by Rauh et al (2011). These issues, along with the other issues raised by various commenters and independent experts, need to be resolved before the Columbia study can be used, if at all, as the basis for regulatory decisions. The Columbia study researchers providing a complete set of all the raw data suitably marked or coded, and not just summaries or selective data, is a necessary step for further analysis and validation.

The analysis included in the TERA report focuses on the impact that missing data and different approaches to plotting data can have on the Columbia study's conclusions and strength of any trends reported. The statistical considerations and approaches to how cognitive testing results are analyzed and interpreted related to epidemiology studies which make reference to chlorpyrifos have also been previously reviewed and challenged (Edwards et al. 2013). The underpinning common denominator here is that whether it be replotting of data points, statistical comparisons, or other experimental variables which influence interpretation, the raw data availability and transparency of those data, while honoring confidentiality, are needed to reach objective, consistent, reliable, scientifically valid, and biologically plausible interpretations regarding exposure and effect. This is especially true of studies which cannot otherwise be repeated, or which are not consistent with the body of experimental and human data available on chlorpyrifos are needed to reach objective, consistent, and biologically plausible interpretations regarding exposure and effect.

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II. Report: A Commentary on Some Epidemiology Data for Chlorpyrifos

INDEPENDENT
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A nonprofit corporation dedicated to the best use of toxicity data for risk values

A Commentary on Some Epidemiology Data for Chlorpyrifos

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Toxicology Excellence for Risk Assessment (*TERA*) is a 501c3 nonprofit organization with a mission to protect public health.

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Summary

Rauh et al. (2011), one of the published studies from the Columbia Center for Children's Environmental Health (CCCEH), claimed statistically significant associations for some reported neurological effects in children with detection of low levels of chlorpyrifos (CPF) in cord blood at the time of birth. It is stated that the mothers may have been exposed to residential uses of chlorpyrifos sometime during pregnancy. These reported effects are surprising in light of the extensive animal and human studies on chlorpyrifos that point to changes in a blood enzyme as its first biological effect, occurring at much higher levels. The chlorpyrifos-specific neurodevelopmental findings reported in the CCCEH have not been replicated in other epidemiology publications, nor have the data on which these publications depend been made available to government scientists for independent confirmation, despite the fact that the CCCEH was supported in part by public funds and the data have been requested by the U.S. Environmental Protection Agency (EPA).

Specifically, Rauh et al. (2011) reported evidence of deficits in Working Memory Index[1] and Full-Scale IQ in children at 7 years old as a function of prenatal CPF exposure. Although these data have not been made available, we were able to extract them in part through an analysis of Figures 1A and 1E of Rauh et al. (2011). This analysis uncovered a surprising fact. Data from approximately 35% of the 265 children described in the text of Rauh et al. (2011) were missing from Figure 1A; approximately 15% of these data were missing from Figure 1E. Although some of the missing data are possibly due to overlay of data points not observable in these published figures, such overlay cannot reasonably account for the extent of these missing data. Further, CCCEH correspondence to EPA admits that data of the four highest exposed children from Rauh et al. (2011) were removed from these figures because at least one data point "drastically impacts inference," suggesting that the statistical significance of these findings may have changed had these data been included.

The data extracted from the figures were analyzed in a number of ways, including a plot of data as response versus log dose, a typical toxicological and risk assessment approach. In contrast to Rauh et al. (2011), our analysis does not suggest any evidence of an effect on Full-Scale IQ (Figure 1E). We also find less of a negative association (reduction) in Working Memory Index (Figure 1A). Obviously, having all of the available data for analysis are preferred, since the lack of raw data from these studies makes statistical analysis and confirmation, a hallmark of scientific inquiry, impossible. The receipt of the raw data would also allow us to consider adjusting responses for other confounding variables, as was done by Rauh et al. (2011). Disclosure of the four truncated data points with the highest chlorpyrifos levels would also permit evaluation of their impact on the interpretation of the claimed association.

In conclusion, the reported associations of chlorpyrifos levels with Working Memory and Full Scale IQ have significant shortcomings and were not replicated in our analysis. The inconsistency with cholinergic responses in other research raises doubts about the validity of the

[1] Working Memory Index assesses children's ability to memorize new information, hold it in short-term memory, concentrate, and manipulate information.

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CCCEH findings.

Introduction

EPA Administrator Pruitt's recent announcement that EPA will be strengthening the transparency in regulatory science or otherwise not using science for which the underlying data cannot be procured, has provoked significant discussion.[2] Much has been made about this new proposed EPA policy, including op-eds against it (e.g., McCarthy and McCabe),[3] and arguments for it based on a risk assessment perspective (e.g., Dourson).[4] All of this discussion serves to focus attention on an important issue. Specifically, how is science considered acceptable and useful in EPA's rulemaking?

In the case of the pesticide chlorpyrifos (CPF), scores of studies[5] suggest that its sentinel[6] effect, that is, the first biological effect (or marker of exposure) or its known precursor, is cholinesterase inhibition, and that this inhibition occurs at roughly the same dose and time course in experimental animals and humans.[7] This finding is so well accepted that health agencies across the world have focused on cholinesterase inhibition as the basis for determining chlorpyrifos' safe dose. Therefore, it came as a surprise to many scientists that Rauh et al. (2011), one of the published studies from the Columbia Center for Children's Environmental Health (CCCEH), claimed neurological effects in children associated with prenatal levels of CPF that were much lower that than those that showed cholinesterase inhibition.[8] The claims reported by Rauh et al, (2011) were in contrast to the weigh-of-evidence of decades of accepted studies on chlorpyrifos, and were used by some to suggest an alternative hypothesis, specifically, that the sentinel effect for chlorpyrifos should be based on human neurological effects rather than cholinesterase inhibition.

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[2] See: https://www.federalregister.gov/documents/2018/04/30/2018-09078/strengthening-transparency-in-regulatory-science).

[3] See: https://www.nytimes.com/2018/03/26/opinion/pruitt-attack-science-epa.html.

[4] See: https://www.washingtonexaminer.com/opinion/op-eds/the-epas-new-secret-science-rule-makes-sense-from-a-risk-assessment-perspective.

[5] U.S. Environmental Protection Agency. 2014. Revised Human Health Risk Assessment for Registration Review. Office of Pesticide Programs, Washington, DC. December 29.

[6] This is also referred to as the chemical's critical effect.

[7] See Zhao et al. 2006. A Review of the Reference Dose (RfD) for Chlorpyrifos. Reg. Toxicol. Pharmacol. 44:111-124.

[8] Rauh et al. (2011). Seven-Year Neurodevelopmental Scores and Prenatal Exposure to Chlorpyrifos, a Common Agricultural Pesticide, Environmental Health Perspectives, Volume 119 (number 8): 1196-1201.

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Specifically, Rauh et al. (2011), show statistically significant, negative associations of Working Memory and Full Scale IQ scores[9] after adjustment by the natural logarithm with dose shown in normal units. This adjustment of the IQ scores compresses the top of the y-axis in relationship to the bottom. This compression of top IQ scores and stretching out of the lower IQ scores gives the subtle appearance of a downward shift, which lessens when IQ scores on the y-axis are not mathematically so adjusted.

From a risk assessment perspective, a more typical data display would be to show unadjusted IQ scores, which are already expected to be normally distributed, as a function of dose that is in either normal units or itself adjusted by logarithm (based 10). Note that the dose x-axis when adjusted into log units will also stretch out the lower part of the axis in relationship to the higher part of the axis. In this case the logarithm adjustment is appropriate, however, because most of the exposure data lie in the lower part of the dose x-axis.

The purpose of this white paper is to summarize points to consider when contemplating whether or not this alternative hypothesis is supportable by analysis of the available data from these epidemiology findings, and in light of the more extensive CPF human/animal database.

Methods

Figures 1A (Working Memory) and 1E (Fill Scale IQ) of Rauh et al. (2011) were viewed by TERA scientists and the results for chlorpyrifos levels and test scores entered into an excel spreadsheet for further analysis. For Figure 1A of Rauh et al. (2011), 33 data points were shown by Rauh et al. as zero or non-detectable. For Figure 1E, 60 points were shown as zero or non-detectable. Consistent with the approach of Raul et al. (2011, page 1198), ~80% of these values were assigned a chlorpyrifos level of 0.5 pg/g and ~20% of them were assigned a level of 1.0 pg/g.

The results were then plotted as natural logarithm-adjusted response versus reported dose (as per Rauh et al., 2011), and as un-adjusted response versus $\log_{10}$ dose. Linear regressions were developed using excel spreadsheet software. During this reanalysis, we discovered that approximately 35% of the data, as stated to be available in the publication in Rauh et al. (2011, page 1197), were missing in Figure 1A and approximately15% of the data were missing from Figure 1E, Moreover, four high dose data points were missing in both graphs. The CCCEH response to US EPA staff suggests to us that the inclusion of these four truncated data points would have attenuated or perhaps even eliminated the statistical significance of their findings.[10]

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[9] Each of the measurements in the Rauh et al. (2011) study are a "standardized scale has [with] a mean of 100 and SD of 15." (See Rauh et al. page 1197, column 3, line 16-17.). This means that the y-axis is expected to be a normal bell-shaped distribution.

[10] Memo to: Carrol Christensen, Ph.D; From: Robin M. Whyatt, DrPH; Date: April 9, 2015
Re: July 2011 letter to Deborah Smegal, M.P.H.: [Full memo available as Appendix A]

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Furthermore, our examination of Figure 1A in Rauh et al. (2011) revealed a tremendous amount of scatter at CPF blood concentrations of 5 pg/g or less, but little scatter at higher blood levels. Consequently, it would seem reasonable to include these 4 data points in the higher blood concentration range in any calculation.

Results

Figure 1 is taken from the Rauh et al. (2011) publication, specifically their Figure 1A (Working Memory). Figure 2 attempts to replicate the Rauh et al. Figure 1. This replication seems reasonable from a comparison of where the regression lines lie in relationship to the high dose points in either figure, despite the fact that we are missing approximately 35% of the data stated to be available in Rauh et al. (2011) (see Appendix B for our raw data and Appendix C for a comparison between data sets). However, and importantly, Rauh et al. also do not include high dose data on their charts (e.g., see reference to 63 pg/g on Rauh et al. page 1198, column 2, which is not found on Figure 1A). Apparently also missing is one child with a value of 32 pg/g (see stated CPF range in Rauh et al., Table 1).

EPA comment: In Figure 1 page 29, the upper bound of the x axis (chlorpyrifos) is shown to be 25 pg/gm. However, in the second paragraph of page 11 it was reported that the maximum CPF exposure is 63 pg/g. It was not clear to us why in Figure 1 the range of CPF was truncated.

CCCEH response: The maximum CPF exposure in the sample was indeed 63 pg/g. The number of children with CPF levels above 25 pg/g were 4. The x-axis was truncated at 25 pg/gm for the following reasons:

1) One of the subjects did not have the outcomes measured.

2) The subject with 63 pg/g was a highly influential observation (outlier) and drastically impacts inference. This was confirmed based on residual analysis in most analyses. Where appropriate, this observation was removed from the analysis. This influence was observed in the spline plots as well and this lone outlier at the extreme end of the exposure made the plot unstable and uninformative.

3) With just two observation left in this range, the data were too sparse and the splines too unstable in this region.

Moreover, being exploratory in nature, the spline plots were constructed to assess the adequacy of a linear relationship between log-transformed CPF and WISC scores. We therefore restricted the splines to the range of CPF values were the data were not sparse and the curves were stable.

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Figure 1. Ln Working Memory Index Versus Dose of Rauh et al. (2011, Figure 1A).

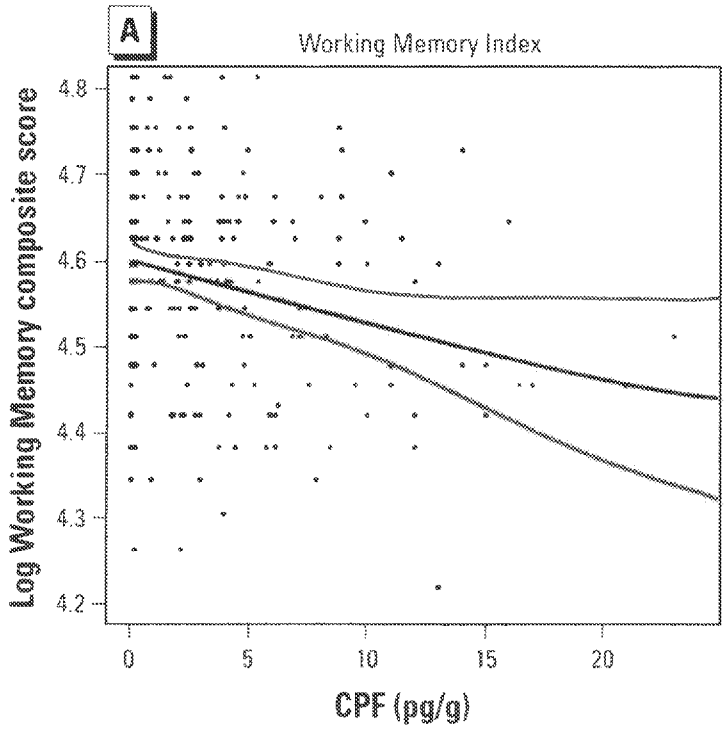

Figure 2. Ln Working Memory Index Versus Dose

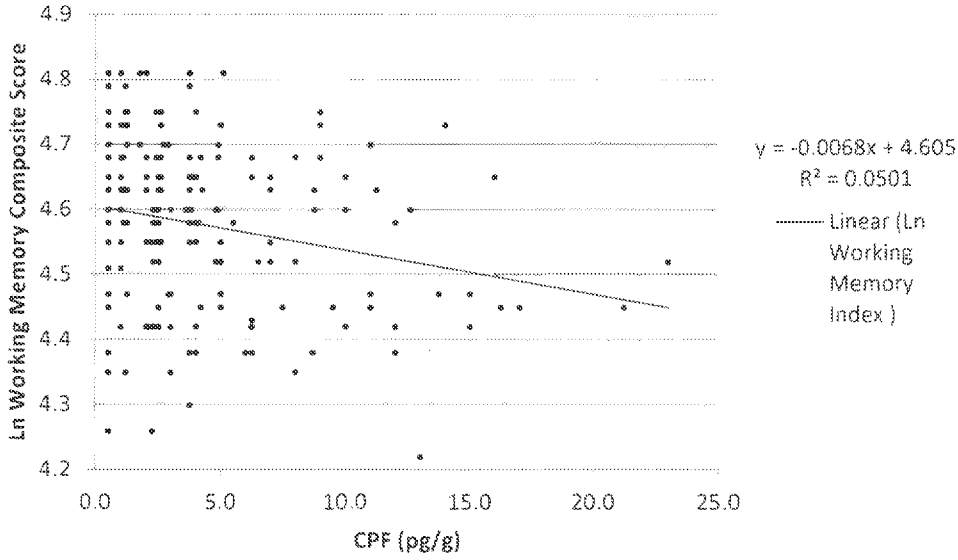

Figure 3. Working Memory Index Versus Log10 Dose

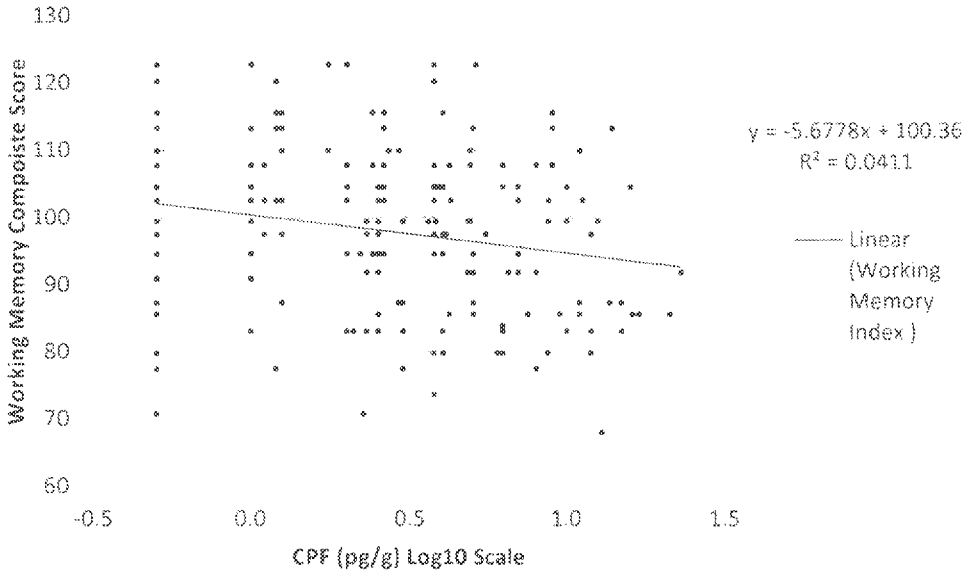

Figure 3 reflects the data from Figure 2 plotted with the response unadjusted and the dose in logarithmic units ($\log_{10}$). Figure 3 shows a reduced effect on Working Memory Index when compared with Figure 2, found by comparing where the regression lines lie in relationship to high dose data points. This indicates that the way Rauh et al. (2011) presented the data had an effect on interpretation. Moreover, the response y-axis is not compressed in our Figure 3, eliminating the subtle visual effect of downward trend due to this compression of the y-axis found in Figure 2. The R^2 for both regression lines are very small, which indicates that chlorpyrifos does not well explain the data variability (i.e. the scatter).

Figure 4 is from Rauh et al. (2011), specifically their Figure 1E (Full Scale IQ). Figure 5 here attempts to replicate these findings. This replication is not as close as Figures 1 and 2. (Again, compare where the regression lines lie in relationship to high dose points in either Figure 4 or 5.) As in the previous comparison of Figures 1-3, some of the data stated to be available in Rauh et al. (2011) are missing (in this case approximately 15%; see Appendix B for our raw data).

Figure 6 reflects the data from Figure 5 plotted with the response unadjusted and the dose in logarithmic units ($\log_{10}$). Figure 6 shows no effect on Full Scale Composite score when compared with Figure 5. As before, the y-axis is not compressed in our Figure 6, eliminating the subtle visual effect of downward trend due to this compression in the y-axis of Figure 5. The R^2 is for Full Scale IQ is even smaller than for Working Memory, suggesting that chlorpyrifos is a poor predictor of the outcome.

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Figure 4. Ln Working Full-Scale IQ Versus Dose of Rauh et al. (2011, Figure 1E).

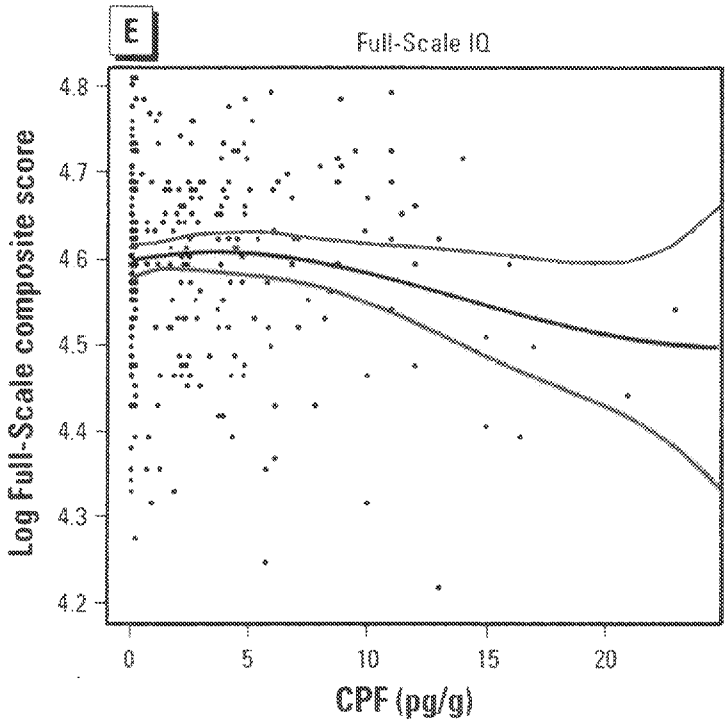


Figure 5. Ln Full Scale IQ Versus Dose

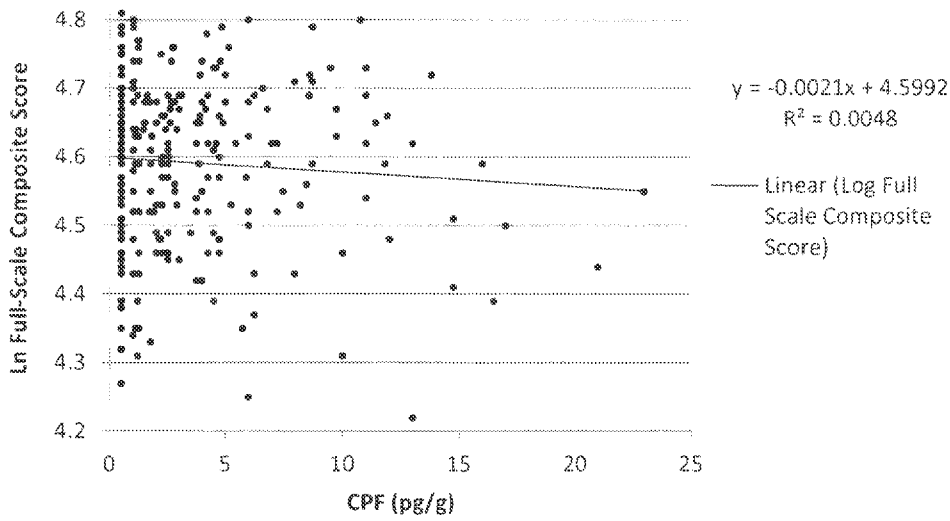
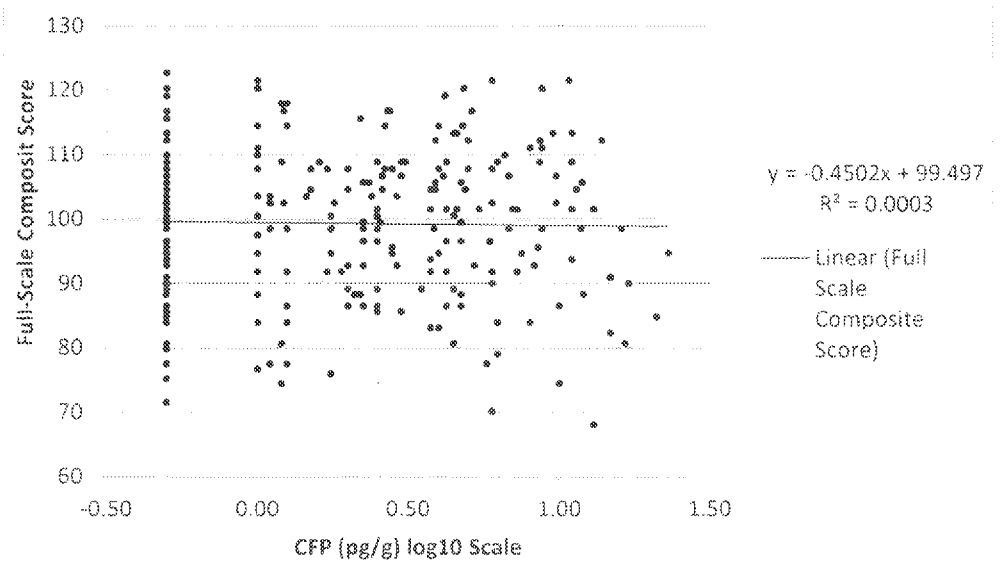


Figure 6. Full Scale IQ Versus Log10 Dose



The bottom line of this simple reanalysis is that evidence of effect for Full-Scale IQ does not exist when the study data are presented in another manner (Figure 6). Working Memory shows evidence of a negative statistical association with dose (Figure 3), but this evidence is problematic due to missing data, including data for the highest exposed individual that Rauh et al. (2011) state "was a highly influential observation (outlier) and drastically impacts inference."

Overall, the lack of raw data from this study makes statistical analysis and confirmation of the authors' data and results, a hallmark of scientific inquiry, impossible.

Discussion

The most significant challenge, by far, in any reanalysis of the Rauh et al. (2011) study is the absence of data to conduct a credible replication to confirm the data analysis. For example, Rauh et al. (2011) state that:

> "Of 725 consenting women, 535 were active participants in the ongoing cohort study at the time of this report, and 265 of their children had reached the age of 7 years with complete data on the following: *a*) prenatal maternal interview data, *b*) biomarkers of prenatal CPF exposure level from maternal and/or cord blood samples at delivery, *c*) postnatal covariates, and *d*) neurodevelopmental outcomes."

However, the Results section of Rauh et al. (2011) show a series of 5 graphs, each of which

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would be expected to offer a complete picture of effects based on 265 children (as suggested from the quotation above). Yet, our analysis of two of these graphs (Figures 1A and 1E) show ~35% or ~15% missing data points, respectively, and neither of these graphs include the data points from the highest cord blood CPF exposures of 63 pg/g, or another higher dose data point of 32 pg/g, as stated by Rauh et al. (2011, Table 1) (see Appendix B for our raw data).

Despite these missing data, what do our analyses show? Although negative neurological associations are reported in the Rauh et al. (2011) with CPF exposure when a plot of Working Memory Composite Scores are normalized by their natural logarithm, and plotted against dose, this manner of data display is not the only one possible. A standard risk assessment approach would be to plot the unadjusted scores, which are already expected to be normally distributed in the human population (as per Rauh et al., 2011 Experimental Design), against the logarithm of dose.

When the results of Rauh et al. (2011) are plotted using logarithmic scales in this way, a reduced association is found. For example, Figure 2 is a representation of Rauh et al.'s Figure 1A (shown here as Figure 1) plotted as the natural logarithm of response versus dose. Figure 3 shows these same data, but where the response, Working Memory, is plotted as unadjusted response versus $\log_{10}$ dose. A comparison of Figures 2 and 3 will show that the negative trend of Figure 2 for the Working Memory is less in Figure 3. When a similar analysis is performed for Full Scale IQ (or Composite Score) the slight negative trend of Figure 5, which is a representation of Rauh et al. (2011) Figure 1E and shown here as Figure 4, disappears; compare Figures 5 and 6.[11]

Whether one method of plotting these data is superior to another may be important, but a strong true association should not be affected by the method of data plotting. A more appropriate, scientific approach to confirm our findings would be to have access to the underlying raw data. For example, access to the raw data would enable us to discuss our results in more statistical terms, by comparing the differences in the slopes of the regressions and the low r^2 values. This would allow a stronger statement on whether a statistical significant association is found (or not). Further, access to the raw data would allow us and others to adjust for confounding factors as was performed by Rauh et al. (2011) in their regression. Moreover, we might be able to refine our analysis from a simple linear approach to an alternate approach in a manner similar to that shown by Rauh et al. (2011) who presented a smooth cubic spine curve.

[11] What about including the missing high dose data? Adding the two high dose data points described in Rauh et al. (2011) to figures 3 and 6 and supposing only average responses further decrease the negative slopes, but only slightly (data not shown). This indicates even less of an effect, if any, from chlorpyrifos exposure.

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We acknowledge that our analysis from published graphs is a rudimentary way to obtain the raw data of Rauh et al. (2011), because data points may often overlay one another in published figures.[12] Still, such an analysis of the Rauh et al. (2011) data shows that no CPF exposures greater than 25 pg/g are plotted. So, where are these high dose data described by Rauh et al. (2011)?

Not surprisingly, as co-sponsors of the study, scientists with the EPA have asked for the raw data from Rauh et al. (2011) and earlier publications.[13] Such a request would seem reasonable, because as described by Rauh and coworkers:

> "This study was supported by the National Institute of Environmental Health Sciences (grants 5P01ES09600, P50ES015905, and 5R01ES08977), the U.S. Environmental Protection Agency (grants R827027, 8260901, and RR00645), the Educational Foundation of America, the John and Wendy Neu Family Foundation, the New York Community Trust, and the Trustees of the Blanchette Hooker Rockefeller Fund."

As EPA has noted in its request for the raw data, its scientists are familiar with rules for handling confidential data. Moreover, personal information of the subjects can be redacted while maintaining the ability to replicate findings.

Unfortunately, the raw data have not been forthcoming.

A number of additional questions or comments can be raised with regard to this epidemiology study. For example:

- How is it that the full scale composite score graph of Rauh et al. (2011; Figure 1 E) has more data points than Rauh et al. (2011) graph of working memory composite score (Figure 1A), if the former depends on the latter?

- According to Rauh et al. (2011), umbilical cord blood samples were not collected at birth in 12% of the study population. Nor were prenatal blood lead levels, a known neurological risk for children, collected for 66% of the maternal study population. In addition, blood lead samples were only collected in 89 out of 265 children, or 34%.

- Epidemiologists often study associations among a plethora of effects versus exposures to multiple chemicals. This is a good strategy since associations can lead to further, more definitive, investigations, based on a more clearly defined hypothesis. The hypothesis

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[12] It is essentially impossible that all of the missing data points in the Rauh et al. (2011) Figures 1A and 1E are underneath the other points. One point is ~0.01% of the graph area and all data points combined covers less than ~2% of the graph area. There are 265 children in the study, but only approximately 170 data points observable in Figure 1A. Thus, the chance that all of the missing data points are hidden below other data points is miniscule. Rather it appears that many of these data points were not added to these figures.

[13] US EPA. 2014. Chlorpyrifos: Revised Human Health Risk Assessment for Registration Review. Appendix 6, page 384 and Addendum, page 394. December 29.

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developed from the Rauh et al. (2011) study, in particular, would be that neurological effects occur at doses lower than cholinesterase inhibition. This hypothesis can be tested…

- …And it has been tested with CPF in a number of experimental animals, and found not to be supported. Specifically, neurological effects do occur in experimental animals, but only at doses that exceed those which cause cholinesterase inhibition in the experimental animals (EPA, 2014). Although it may be that these experimental animal studies are not able to monitor for the types of neurological effects associated with increasing CPF dose in Rauh et al. (2011) and related studies, the observed neurological effects in experimental animals are more than 100-fold greater on the dose scale than the purported epidemiology associations. This disparity in dose makes it difficult to accept the epidemiological associations as credible, especially when human and experimental animal studies are similar in dose with respect to cholinesterase inhibition, the current sentinel or critical effect for CPF as demonstrated by Zhao et al., (2006). Should one expect that neurological effects would differ in the dose scale between experimental animals and humans, when the critical effect, cholinesterase inhibition, does not?

- The metabolite responsible for the toxicity of cholinesterase inhibition, CPF-oxon, is formed in the liver and 99% of this oxon derivative irreversibly binds to cholinesterase in the blood at levels (EPA, 2014). Since it is so bound, it would not be expected to reach the brain to affect neurological development of the fetus at levels much lower than levels which do not otherwise show any effect on the sentinel blood enzyme In fact, an analysis by Marty et al. (2012)[14] showed no systemic bioavailability, nor any brain cholinesterase inhibition with the CPF-oxon at doses comparable to the established safe doses.

- A number of other factors are known to affect neurodevelopmental effects in infants and children. These other documented, potential causes of the effects reported need to be fully evaluated.

- The specific results described by Rauh et al. (2011) are not reproduced in other epidemiology studies, which challenge the claim of a link between neurodevelopment effects and chlorpyrifos exposures. In fact, Burns (2018) shows that consideration of the findings *in total across* these studies does not support and even counters such a claim.[15]

Conclusion

One of the papers from the CCCEH, specifically Rauh et al. (2011), has been cited as showing a statistical association between CPF exposure and intelligence. This study has significant scientific shortcomings. An analysis of the published figures shows that up to 35% of the data

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[14] M.S.Marty, A.K.Andrus, M.P.Bell, J.K.Passage, A.W.Perala, K.A.Brzak, M.J.Bartels, M.J.Beck, D.R.Juberg, Cholinesterase inhibition and toxicokinetics in immature and adult rats after acute or repeated exposures to chlorpyrifos or chlorpyrifos–oxon. Reg. Toxicol. Pharmacol. 63 (2): 209-224. July 2012.

[15] Burns, C.J. 2018. Reproducibility is critical for determining scientific validity. Sanford, MI. June 6.

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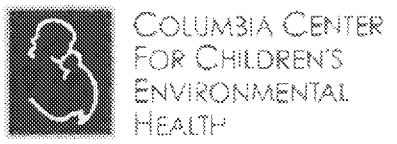
appear to be missing, and that the data adjustment used was not typical from a risk assessment perspective. The associations are lessened or no longer apparent when different logarithmic assumptions were used in the reanalysis. Moreover, the data, generated in part by public funds, have not been made available for independent review. These shortcomings make it difficult to confirm this study's findings and raise serious scientific doubt about the validity of the published results.

Appendix A



MAILMAN SCHOOL OF PUBLIC HEALTH
Columbia University

Memo to: Carol Christensen, Ph.D
From: Robin M. Whyatt, DrPH
Date: April 9, 2015

Re: July 2011 letter to Deborah Smegal, M.P.H.

In reading through the 2014 chlorpyrifos risk assessment document, we were pleased to see that it contained almost all of our correspondence answering questions from both the SAP and EPA on our various chlopyrifos articles. However, the letter we prepared answering a series of questions from Deborah Smegal, MPH, on our 2011 manuscript[1] was not included in document and, we believe, should also be part of the docket. As you will see, the letter first lists each question from Ms. Smegal followed by our answers to that question. Please let us know if you have any questions.

[1]Rauh V, Arunajadai S, Horton M, Perera F, Hoepner L, Barr DB, Whyatt R. Seven-year neurodevelopmental scores and prenatal exposure to chlorpyrifos, a common agricultural pesticide, Environ Health Perspect. 119(8): 1196-201, 2011. PMCID: PMC3237355

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Dear Debbie,

The questions are quite straight-forward , so hopefully this will clarify your reading of the results. The important point is that we have modest yet meaningful findings that are consistent across several different analytic approaches. We note that you have suggested other statistical approaches, such as generalized Linear Model, which is typically employed in situations where departures from normality are more extreme than the present case. It is always a judgment call to select the single 'best' approach . Thank you for pointing out the one digit error in the on line version of the paper (Table 2), and this has been corrected in the final version . Otherwise, please let us know if you have additional questions

1 The paper reports the decline of IQ and Working memory in terms of 1 standard deviation increase of CPF However it is recognized that usually chlorpyrifos exposure follows log- normal distribution. Infect the authors made the same distributional assumption of CPF while imputing the non-detects. It would be more helpful for interpretation purposes to express the decline of IQ and Working memory in terms of geometric standard deviation of CPF instead of arithmetic standard deviation In table 9 2 of page 262 of Environmental Statistics and Data Analysis by Wayne R Ott relationship between arithmetic parameters (mean and standard deviation) and geometric parameters (mean and standard deviation) were provided Using these transformation CEB found that 1 geometric standard deviation increase of CPF prenatal exposure will decrease the full scale IQ by 0 87 % and working memory by 1 73%

We are not sure how exactly the calculations above were done. We computed the Geometric Mean (GM) and Geometric Standard Deviation (GSD) of the Chlorpyrifos exposure from the data and were found to be 0.65 and 6.22 respectively. Thus for one GSD increase in CPF, the Fu ll Scale IQ on average decreases by 1 85% and Working Memory by 3 66%

2 In Figure 1 page 29, the upper bound of the x axis(Chlorpyrifos) is shown to be 25 pg/gm However in the second paragraph of page 11 it was reported that the maximum CPF exposure is 63 pg/g It was not clear to us why in figure 1 the range of CPF was truncated

The maximum CPF exposure in the sample was indeed 63 pg/g . The number of children with CPF levels above 25 pg/g were 4. The x-axis was truncated at 25 pg/gm for the following reasons
1) One of the subjects did not have the outcomes measured
2) The subject with 63 pg/g was a highly influential observation (outlier) and drastically impacts inference. This was confirmed based on residual analysis in most analyses Where appropriate this observation was removed from the analysis. This influence was observed in the spline plots as well and this lone outlier at the extreme end of the exposure made the plot unstable and uninformative
3) With just two observation left in this range, the data were too sparse and the splines too unstable in this region .

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Moreover, being exploratory in nature, the spline plots were constructed to assess the adequacy of a linear relationship between log-transformed CPF and WISC scores. We therefore restricted the splines to the range of CPF values were the data were not sparse and the curves were stable.

3. In table-2 for the fully adjusted model of Full scale IQ the 95% confidence interval for the coefficient of CPF includes 0. Therefore the CPF is not statistically associated with Full scale IQ based on C. I. However the p value for the same coefficient is shown to be less than 0.05. It is statistically impossible to have p value less than 0.05 and 95% confidence interval includes 0 at the same time. The author should explain this inconsistency between the p value and the C.I -- perhaps this inconsistency is simply due to round ing?

The Fully adjusted coefficients in Table 2 should have values consistent with the values in the supplementary material Table 1. Thus for Full scale IQ , rounded to three significant digits, the 95% CIs were -0. 006 to 0.000, and the p-value rounded to 2 decimal places is equal to 0.05 (0.048). The values in table 2 in the main paper should have read -0. 006, 0.000 as opposed to -0.006, 0.001 . Thanks so much for picking up this incorrect digit.

4. Using Lasso model, it was shown in Table 2 that prenatal exposure and Full scale IQ is not statistically associated at alpha=0.05 level. However in the result section of the abstract it was stated that for each standard deviation increase in exposure of CPF full scale IQ declined by 1.4. The paper should include a discussion about non significance of prenatal exposure of CPF for the Full scale IQ when interpreting the association between IQ and CPF exposure

We direct the reader to the comparability of the LASSO and the fully adjusted models in terms of effect size (coefficient). The fully adjusted model is the more famil iar approach to regression analysis, and includes all of the covariates. We were interested in using LASSO to demonstrate that the effect sizes do not vary in a meaningful way, using a procedure that may be less vulnerable to over-fitting . In interpreting the results , the effect size may be more important than statistical significance alone, as the significance can be affected by sample size and power. Specifically, when sample size and power are modest, the results of significance tests can be misleading because of being subject to Type II errors (incorrectly failing to reject the null hypothesis). In these situations, it can be more informative to use the effect sizes (how much of an effect), especially with the confidence intervals.

5. The authors stated in the data analysis section of page 9 that WISC-IV composite index scores have been log transformed to stabi lize the variance and to improve the linear model fit. Another alternate approach may be to use the generalized linear model which may be better able to deal with the issues of concern

The intention here is to investigate the shape and the strength of the possible doseeffect relationship. While a Generalized Linear Model might also be used , log transformation usually provides consistent results when we have normal residuals (as we do here). Generalized Linear Models are a kind of extension of the linear modeling process that allows models to be fit to data that follow probability distributions other than

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the Normal distribution, such as the Poisson, Binomial, Multinomial, and etc. Generalized Linear Models also relax the requirement of equality or constancy of variances that is required for hypothesis tests in traditional linear models. While it is certainly possible to use Generalized Linear Models (and there are many different ways to test our hypotheses), there is no indication that this procedure would result in a better fit or a more precise estimate.

Appendix B: TERA Reading of Rauh et al. (2011) Figure 1A

The first 33 points are zero or non-detectable and have been assigned chlorpyrifos levels with Rauh et al. 2011 page 1198. Specifically 80% at 0.5pg/g and 20% 1.0pg/g. This set of data points was manually read from Figure 1A Rauh et al. (2011).

CPN (pg/g)	log Chlorpyrifos (pg/g)	ln Chlorpyrifos (pg/g)	ln Working Memory Index	Working Memory Index	Probits
0.5	-0.3	-0.7	4.26	71	-1.95
0.5	-0.3	-0.7	4.35	77	-1.50
0.5	-0.3	-0.7	4.38	80	-1.34
0.5	-0.3	-0.7	4.38	80	-1.34
0.5	-0.3	-0.7	4.45	86	-0.96
0.5	-0.3	-0.7	4.47	87	-0.84
0.5	-0.3	-0.7	4.47	87	-0.84
0.5	-0.3	-0.7	4.51	91	-0.61
0.5	-0.3	-0.7	4.55	95	-0.36
0.5	-0.3	-0.7	4.55	95	-0.36
0.5	-0.3	-0.7	4.58	98	-0.17
0.5	-0.3	-0.7	4.58	98	-0.17
0.5	-0.3	-0.7	4.6	99	-0.03
0.5	-0.3	-0.7	4.63	103	0.17
0.5	-0.3	-0.7	4.63	103	0.17
0.5	-0.3	-0.7	4.65	105	0.31
0.5	-0.3	-0.7	4.68	108	0.52
0.5	-0.3	-0.7	4.68	108	0.52
0.5	-0.3	-0.7	4.7	110	0.66
0.5	-0.3	-0.7	4.7	110	0.66
0.5	-0.3	-0.7	4.73	113	0.89
0.5	-0.3	-0.7	4.75	116	1.04
0.5	-0.3	-0.7	4.75	116	1.04
0.5	-0.3	-0.7	4.79	120	1.35
0.5	-0.3	-0.7	4.81	123	1.52
1.0	0.0	0.0	4.42	83	-1.13
1.0	0.0	0.0	4.51	91	-0.61
1.0	0.0	0.0	4.55	95	-0.36
1.0	0.0	0.0	4.6	99	-0.03

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CPN (pg/g)	log Chlorpyrifos (pg/g)	ln Chlorpyrifos (pg/g)	ln Working Memory Index	Working Memory Index	Probits
1.0	0.0	0.0	4.65	105	0.31
1.0	0.0	0.0	4.68	108	0.52
1.0	0.0	0.0	4.73	113	0.89
1.0	0.0	0.0	4.81	123	1.52
2.25	0.1	0.2	4.26	71	-1.95
13	1.1	2.6	4.22	68	-2.13
3.75	0.6	1.3	4.3	74	-1.75
8	0.9	2.1	4.35	77	-1.50
3	0.5	1.1	4.35	77	-1.50
1.2	0.1	0.2	4.35	77	-1.50
12	1.1	2.5	4.38	80	-1.34
8.7	0.9	2.2	4.38	80	-1.34
6.25	0.8	1.8	4.38	80	-1.34
6	0.8	1.8	4.38	80	-1.34
4	0.6	1.4	4.38	80	-1.34
3.75	0.6	1.3	4.38	80	-1.34
15	1.2	2.7	4.42	83	-1.13
12	1.1	2.5	4.42	83	-1.13
10	1.0	2.3	4.42	83	-1.13
6.25	0.8	1.8	4.42	83	-1.13
6.24	0.8	1.8	4.42	83	-1.13
6.23	0.8	1.8	4.42	83	-1.13
4	0.6	1.4	4.42	83	-1.13
3	0.5	1.1	4.42	83	-1.13
3	0.5	1.1	4.42	83	-1.13
2.5	0.4	0.9	4.42	83	-1.13
2.3	0.4	0.8	4.42	83	-1.13
2	0.3	0.7	4.42	83	-1.13
2.1	0.3	0.7	4.42	83	-1.13
6.25	0.8	1.8	4.43	84	-1.07
21.3	1.3	3.1	4.45	86	-0.96
16.3	1.2	2.8	4.45	86	-0.96
17	1.2	2.8	4.45	86	-0.96
11	1.0	2.4	4.45	86	-0.96
9.5	1.0	2.3	4.45	86	-0.96
7.5	0.9	2.0	4.45	86	-0.96
5	0.7	1.6	4.45	86	-0.96
4.2	0.6	1.4	4.45	86	-0.96

CPN (pg/g)	log Chlorpyrifos (pg/g)	ln Chlorpyrifos (pg/g)	ln Working Memory Index	Working Memory Index	Probits
2.5	0.4	0.9	4.45	86	-0.96
15	1.2	2.7	4.47	87	-0.84
13.8	1.1	2.6	4.47	87	-0.84
11	1.0	2.4	4.47	87	-0.84
5	0.7	1.6	4.47	87	-0.84
3	0.5	1.1	4.47	87	-0.84
2.9	0.5	1.1	4.47	87	-0.84
1.25	0.1	0.2	4.47	87	-0.84
23	1.4	3.1	4.52	92	-0.54
8	0.9	2.1	4.52	92	-0.54
7	0.8	1.9	4.52	92	-0.54
6.5	0.8	1.9	4.52	92	-0.54
5	0.7	1.6	4.52	92	-0.54
4.8	0.7	1.6	4.52	92	-0.54
2.5	0.4	0.9	4.52	92	-0.54
2.3	0.4	0.8	4.52	92	-0.54
7	0.8	1.9	4.55	95	-0.36
5	0.7	1.6	4.55	95	-0.36
4	0.6	1.4	4.55	95	-0.36
3.75	0.6	1.3	4.55	95	-0.36
2.6	0.4	1.0	4.55	95	-0.36
2.5	0.4	0.9	4.55	95	-0.36
2.4	0.4	0.9	4.55	95	-0.36
2.2	0.3	0.8	4.55	95	-0.36
2	0.3	0.7	4.55	95	-0.36
1	0.0	0.0	4.55	95	-0.36
1	0.0	0.0	4.55	95	-0.36
12	1.1	2.5	4.58	98	-0.17
5.5	0.7	1.7	4.58	98	-0.17
3.75	0.6	1.3	4.58	98	-0.17
4	0.6	1.4	4.58	98	-0.17
4.1	0.6	1.4	4.58	98	-0.17
2.5	0.4	0.9	4.58	98	-0.17
2.3	0.4	0.8	4.58	98	-0.17
1.25	0.1	0.2	4.58	98	-0.17
1.1	0.0	0.1	4.58	98	-0.17
12.6	1.1	2.5	4.6	99	-0.03
10	1.0	2.3	4.6	99	-0.03

CPN (pg/g)	log Chlorpyrifos (pg/g)	ln Chlorpyrifos (pg/g)	ln Working Memory Index	Working Memory Index	Probits
8.75	0.9	2.2	4.6	99	-0.03
4.9	0.7	1.6	4.6	99	-0.03
4.8	0.7	1.6	4.6	99	-0.03
3.8	0.6	1.3	4.6	99	-0.03
2.5	0.4	0.9	4.6	99	-0.03
3	0.5	1.1	4.6	99	-0.03
3.6	0.6	1.3	4.6	99	-0.03
2.3	0.4	0.8	4.6	99	-0.03
11.3	1.1	2.4	4.63	103	0.17
8.75	0.9	2.2	4.63	103	0.17
7	0.8	1.9	4.63	103	0.17
3.75	0.6	1.3	4.63	103	0.17
4.25	0.6	1.4	4.63	103	0.17
2.5	0.4	0.9	4.63	103	0.17
2.6	0.4	1.0	4.63	103	0.17
1.25	0.1	0.2	4.63	103	0.17
1.2	0.1	0.2	4.63	103	0.17
2	0.3	0.7	4.63	103	0.17
1	0.0	0.0	4.63	103	0.17
1.1	0.0	0.1	4.63	103	0.17
16	1.2	2.8	4.65	105	0.31
10	1.0	2.3	4.65	105	0.31
6.25	0.8	1.8	4.65	105	0.31
7	0.8	1.9	4.65	105	0.31
3.75	0.6	1.3	4.65	105	0.31
3.8	0.6	1.3	4.65	105	0.31
3.9	0.6	1.4	4.65	105	0.31
4	0.6	1.4	4.65	105	0.31
2.5	0.4	0.9	4.65	105	0.31
2.6	0.4	1.0	4.65	105	0.31
2	0.3	0.7	4.65	105	0.31
9	1.0	2.2	4.68	108	0.52
8	0.9	2.1	4.68	108	0.52
6.25	0.8	1.8	4.68	108	0.52
4.9	0.7	1.6	4.68	108	0.52
4.2	0.6	1.4	4.68	108	0.52
3.75	0.6	1.3	4.68	108	0.52
2.6	0.4	1.0	4.68	108	0.52

CPN (pg/g)	log Chlorpyrifos (pg/g)	ln Chlorpyrifos (pg/g)	ln Working Memory Index	Working Memory Index	Probits
2.4	0.4	0.9	4.68	108	0.52
2	0.3	0.7	4.68	108	0.52
1.1	0.0	0.1	4.68	108	0.52
11	1.0	2.4	4.7	110	0.66
4.9	0.7	1.6	4.7	110	0.66
2.7	0.4	1.0	4.7	110	0.66
2.9	0.5	1.1	4.7	110	0.66
1.75	0.2	0.6	4.7	110	0.66
1.25	0.1	0.2	4.7	110	0.66
14	1.1	2.6	4.73	113	0.89
9	1.0	2.2	4.73	113	0.89
5	0.7	1.6	4.73	113	0.89
2.6	0.4	1.0	4.73	113	0.89
1.25	0.1	0.2	4.73	113	0.89
1.2	0.1	0.2	4.73	113	0.89
9	1.0	2.2	4.75	116	1.04
4	0.6	1.4	4.75	116	1.04
2.6	0.4	1.0	4.75	116	1.04
2.4	0.4	0.9	4.75	116	1.04
1.25	0.1	0.2	4.75	116	1.04
1.2	0.1	0.2	4.75	116	1.04
3.75	0.6	1.3	4.79	120	1.35
1.2	0.1	0.2	4.79	120	1.35
5.1	0.7	1.6	4.81	123	1.52
3.75	0.6	1.3	4.81	123	1.52
1.75	0.2	0.6	4.81	123	1.52
2	0.3	0.7	4.81	123	1.52

TERA Reading of Rauh et al. (2011) Figure 1E

The first 60 Points are zero or non-detectable and have been assigned chlorpyrifos levels consistent with the Rauh et al. 2011 page 1198. Specifically 80% at .05pg/g and 20% 1.0 pg/g. This set of data points was manually read from Figure 1E of Rauh et al. (2011).

Chlorpyrifos (pg/g)	log Chlorpyrifos (pg/g)	ln Chlorpyrifos (pg/g)	ln Full Scale Composite Score	Full Scale Composite Score
0.5	-0.30	-0.7	4.27	72
0.5	-0.30	-0.7	4.32	75
1	0.00	0.0	4.34	77
0.5	-0.30	-0.7	4.35	77
0.5	-0.30	-0.7	4.38	80
0.5	-0.30	-0.7	4.39	81
0.5	-0.30	-0.7	4.43	84
1	0.00	0.0	4.43	84
0.5	-0.30	-0.7	4.44	85
0.5	-0.30	-0.7	4.45	86
0.5	-0.30	-0.7	4.46	86
0.5	-0.30	-0.7	4.46	86
1	0.00	0.0	4.48	88
0.5	-0.30	-0.7	4.48	88
0.5	-0.30	-0.7	4.49	89
0.5	-0.30	-0.7	4.5	90
0.5	-0.30	-0.7	4.51	91
1	0.00	0.0	4.52	92
0.5	-0.30	-0.7	4.53	93
0.5	-0.30	-0.7	4.53	93
0.5	-0.30	-0.7	4.54	94
0.5	-0.30	-0.7	4.55	95
1	0.00	0.0	4.55	95
0.5	-0.30	-0.7	4.56	96
0.5	-0.30	-0.7	4.56	96
0.5	-0.30	-0.7	4.57	97
0.5	-0.30	-0.7	4.57	97

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Chlorpyrifos (pg/g)	log Chlorpyrifos (pg/g)	ln Chlorpyrifos (pg/g)	ln Full Scale Composite Score	Full Scale Composite Score
1	0.00	0.0	4.58	98
0.5	-0.30	-0.7	4.59	98
0.5	-0.30	-0.7	4.59	98
0.5	-0.30	-0.7	4.6	99
0.5	-0.30	-0.7	4.61	100
1	0.00	0.0	4.61	100
0.5	-0.30	-0.7	4.62	101
0.5	-0.30	-0.7	4.62	101
0.5	-0.30	-0.7	4.63	103
0.5	-0.30	-0.7	4.63	103
1	0.00	0.0	4.64	104
0.5	-0.30	-0.7	4.64	104
0.5	-0.30	-0.7	4.65	105
0.5	-0.30	-0.7	4.66	106
0.5	-0.30	-0.7	4.67	107
1	0.00	0.0	4.68	108
0.5	-0.30	-0.7	4.68	108
0.5	-0.30	-0.7	4.69	109
0.5	-0.30	-0.7	4.69	109
0.5	-0.30	-0.7	4.7	110
1	0.00	0.0	4.71	111
0.5	-0.30	-0.7	4.72	112
0.5	-0.30	-0.7	4.72	112
0.5	-0.30	-0.7	4.73	113
0.5	-0.30	-0.7	4.73	113
1	0.00	0.0	4.74	114
0.5	-0.30	-0.7	4.75	116
0.5	-0.30	-0.7	4.76	117
0.5	-0.30	-0.7	4.78	119
0.5	-0.30	-0.7	4.79	120
1	0.00	0.0	4.8	122
0.5	-0.30	-0.7	4.81	123
0.5	-0.30	-0.7	4.81	123
13	1.11	2.6	4.22	68
6	0.78	1.8	4.25	70
10	1.00	2.3	4.31	74
1.2	0.08	0.2	4.31	74
1.75	0.24	0.6	4.33	76

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Chlorpyrifos (pg/g)	log Chlorpyrifos (pg/g)	ln Chlorpyrifos (pg/g)	ln Full Scale Composite Score	Full Scale Composite Score
5.75	0.76	1.7	4.35	77
1.25	0.10	0.2	4.35	77
1.1	0.04	0.1	4.35	77
6.25	0.80	1.8	4.37	79
16.5	1.22	2.8	4.39	81
4.5	0.65	1.5	4.39	81
1.2	0.08	0.2	4.39	81
14.75	1.17	2.7	4.41	82
4	0.60	1.4	4.42	83
3.75	0.57	1.3	4.42	83
8	0.90	2.1	4.43	84
6.25	0.80	1.8	4.43	84
1.25	0.10	0.2	4.43	84
21	1.32	3.0	4.44	85
3	0.48	1.1	4.45	86
2.5	0.40	0.9	4.45	86
10	1.00	2.3	4.46	86
4.75	0.68	1.6	4.46	86
4.25	0.63	1.4	4.46	86
2.5	0.40	0.9	4.46	86
2.25	0.35	0.8	4.46	86
2	0.30	0.7	4.46	86
1.25	0.10	0.2	4.46	86
12	1.08	2.5	4.48	88
4.75	0.68	1.6	4.48	88
2.2	0.34	0.8	4.48	88
2.1	0.32	0.7	4.48	88
4.5	0.65	1.5	4.49	89
3.5	0.54	1.3	4.49	89
2.5	0.40	0.9	4.49	89
2	0.30	0.7	4.49	89
17	1.23	2.8	4.5	90
6	0.78	1.8	4.5	90
14.75	1.17	2.7	4.51	91
7.25	0.86	2.0	4.52	92
6	0.78	1.8	4.52	92
4.25	0.63	1.4	4.52	92
3.75	0.57	1.3	4.52	92

Chlorpyrifos (pg/g)	log Chlorpyrifos (pg/g)	ln Chlorpyrifos (pg/g)	ln Full Scale Composite Score	Full Scale Composite Score
1.9	0.28	0.6	4.52	92
1.7	0.23	0.5	4.52	92
1.25	0.10	0.2	4.52	92
8.25	0.92	2.1	4.53	93
5.25	0.72	1.7	4.53	93
2.9	0.46	1.1	4.53	93
2.25	0.35	0.8	4.53	93
2	0.30	0.7	4.53	93
11	1.04	2.4	4.54	94
3.75	0.57	1.3	4.54	94
23	1.36	3.1	4.55	95
7.5	0.88	2.0	4.55	95
4	0.60	1.4	4.55	95
2.8	0.45	1.0	4.55	95
1.75	0.24	0.6	4.55	95
8.5	0.93	2.1	4.56	96
2.8	0.45	1.0	4.56	96
5.9	0.77	1.8	4.57	97
4.75	0.68	1.6	4.57	97
4.25	0.63	1.4	4.57	97
2.5	0.40	0.9	4.57	97
2.25	0.35	0.8	4.57	97
16	1.20	2.8	4.59	98
11.8	1.07	2.5	4.59	98
8.75	0.94	2.2	4.59	98
6.8	0.83	1.9	4.59	98
3.85	0.59	1.3	4.59	98
2.5	0.40	0.9	4.59	98
2.25	0.35	0.8	4.59	98
1.75	0.24	0.6	4.59	98
1.25	0.10	0.2	4.59	98
1.1	0.04	0.1	4.59	98
4.75	0.68	1.6	4.6	99
2.55	0.41	0.9	4.6	99
2.25	0.35	0.8	4.6	99
4.5	0.65	1.5	4.61	100
2.5	0.40	0.9	4.61	100
1.75	0.24	0.6	4.61	100

Chlorpyrifos (pg/g)	log Chlorpyrifos (pg/g)	ln Chlorpyrifos (pg/g)	ln Full Scale Composite Score	Full Scale Composite Score
13	1.11	2.6	4.62	101
11	1.04	2.4	4.62	101
7.25	0.86	2.0	4.62	101
7	0.85	1.9	4.62	101
5.45	0.74	1.7	4.62	101
4.6	0.66	1.5	4.62	101
4.25	0.63	1.4	4.62	101
3.75	0.57	1.3	4.62	101
2.5	0.40	0.9	4.62	101
9.75	0.99	2.3	4.63	103
6	0.78	1.8	4.63	103
1.8	0.26	0.6	4.63	103
1.22	0.09	0.2	4.63	103
1.1	0.04	0.1	4.63	103
2.9	0.46	1.1	4.64	104
2.4	0.38	0.9	4.64	104
1.45	0.16	0.4	4.64	104
1.1	0.04	0.1	4.64	104
11.4	1.06	2.4	4.65	105
4.9	0.69	1.6	4.65	105
3.9	0.59	1.4	4.65	105
3.75	0.57	1.3	4.65	105
2.6	0.41	1.0	4.65	105
2	0.30	0.7	4.65	105
1.5	0.18	0.4	4.65	105
11.9	1.08	2.5	4.66	106
4.75	0.68	1.6	4.66	106
3.9	0.59	1.4	4.66	106
2.35	0.37	0.9	4.66	106
2.25	0.35	0.8	4.66	106
9.75	0.99	2.3	4.67	107
6.8	0.83	1.9	4.67	107
4.15	0.62	1.4	4.67	107
3	0.48	1.1	4.67	107
2.6	0.41	1.0	4.67	107
6	0.78	1.8	4.68	108
5	0.70	1.6	4.68	108
4	0.60	1.4	4.68	108

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Chlorpyrifos (pg/g)	log Chlorpyrifos (pg/g)	ln Chlorpyrifos (pg/g)	ln Full Scale Composite Score	Full Scale Composite Score
2.8	0.45	1.0	4.68	108
2.65	0.42	1.0	4.68	108
2	0.30	0.7	4.68	108
1.7	0.23	0.5	4.68	108
1.5	0.18	0.4	4.68	108
11	1.04	2.4	4.69	109
8.6	0.93	2.2	4.69	109
6.25	0.80	1.8	4.69	109
4.25	0.63	1.4	4.69	109
3.1	0.49	1.1	4.69	109
3	0.48	1.1	4.69	109
2.5	0.40	0.9	4.69	109
1.6	0.20	0.5	4.69	109
1.2	0.08	0.2	4.69	109
6.6	0.82	1.9	4.7	110
1	0.00	0.0	4.7	110
8.75	0.94	2.2	4.71	111
8	0.90	2.1	4.71	111
13.8	1.14	2.6	4.72	112
8.65	0.94	2.2	4.72	112
5	0.70	1.6	4.72	112
3.9	0.59	1.4	4.72	112
11	1.04	2.4	4.73	113
9.5	0.98	2.3	4.73	113
4.6	0.66	1.5	4.73	113
4.5	0.65	1.5	4.73	113
4.8	0.68	1.6	4.74	114
4	0.60	1.4	4.74	114
2.65	0.42	1.0	4.74	114
1.25	0.10	0.2	4.74	114
2.2	0.34	0.8	4.75	116
5.15	0.71	1.6	4.76	117
2.75	0.44	1.0	4.76	117
2.7	0.43	1.0	4.76	117
1.22	0.09	0.2	4.76	117
1.25	0.10	0.2	4.77	118
1.2	0.08	0.2	4.77	118
4.2	0.62	1.4	4.78	119

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Chlorpyrifos (pg/g)	log Chlorpyrifos (pg/g)	ln Chlorpyrifos (pg/g)	ln Full Scale Composite Score	Full Scale Composite Score
8.75	0.94	2.2	4.79	120
4.85	0.69	1.6	4.79	120
1	0.00	0.0	4.79	120
10.75	1.03	2.4	4.8	122
6	0.78	1.8	4.8	122

Appendix C

Table of Comparisons of data points in IQ analysis							
	Rauh et al. (2011)			This Analysis		Difference	
	Published	truncated > 25 pg/g	<= LOD	Scanned	<= LOD	Difference	%
Working Memory	265	4	115	170	33	91	35%
Full Scale IQ	265	4	115	222	60	39	15%

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III. Brief on Alternate Explanations for Alleged Effects in the Columbia Study

Alternate Explanations for Alleged Effects in the Columbia Study

Situation overview

Researchers for the Columbia Center for Children's Environmental Health (CCCEH) epidemiology study (the "Columbia study") have claimed in their publications a correlation between levels of chlorpyrifos allegedly found in the umbilical cord blood of a group of mothers almost 20 years ago with neurodevelopmental effects allegedly observed in their children later in life. EPA is proposing to use the findings from the Columbia study as proof of a causal relationship and to then set a new, dramatically lower, regulatory health endpoint or Point of Departure (PoD) for chlorpyrifos based on that study.

Background on Columbia study

The Columbia University researchers have been studying a group of New York City children born between 1998 and 2002. The investigators have followed the health of these inner-city children of African American and Dominican decent for 15 years. The study started by looking at the many problems existing in public housing such as holes in the ceiling, leaking pipes and unrepaired water damage , each reported by more than a third of the mothers, which in turn were associated with cockroach and rodent sightings. Measures of "unmet needs" that included inadequate food, housing or clothing during pregnancy were counted. The investigators also evaluated the education, intelligence, and income of the mothers, which are predictors of childhood development. Unavailable was information about the father, including paternal IQ. From the many publications from the Columbia study it is evident that this is a very disadvantaged group of children.

The Columbia study was designed to look at many environmental factors that may affect childhood health. To this end, the investigators tested the household air and infant cord blood for numerous different chemicals, elements (such as lead), and pesticides. They have multiple publications in the peer-reviewed literature on correlations between a few of these exposure estimates from birth and subsequent development during childhood, but have not yet reported on all.

Claims of health effects in the Columbia study

Publications by the Columbia study researchers noted that by age 2 nearly half of the study children were diagnosed with moderately delayed mental development and many were physically delayed. By age 7, while the mean IQ for the children was average, some were severely mentally challenged. It is worth noting, researchers found the children's IQs are greater on average than their mothers, since the mothers' mean IQ was 85.

Columbia study researchers also published correlations between various neurodevelopment or health effects in the study children with other factors such as phthalates, polycyclic aromatic hydrocarbons, and second-hand tobacco smoke.

Alternate explanations for claimed health effects

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While the Columbia researchers attribute some correlations of lower test scores with higher chlorpyrifos levels, correlation alone does not prove cause and effect, and a causal relationship. Further, EPA even admits, there is no biological explanation, despite numerous attempts to identify one, of how the action of chlorpyrifos in the body would affect neurodevelopment at low levels. The well-documented effect for chlorpyrifos is cholinesterase inhibition not neurodevelopmental effects. Extensive research in both humans and animal clearly show there is no biological plausibility to the claim of a cause and effect between exposure to chlorpyrifos and findings reported in the Columbia study.

It is important to understand that many factors can influence childhood development – both for better or worse and could also be correlated with the effects reported.

- Characteristics at birth, with gestational age (being born too early) being most notable among the explanations for the effects on the test scores reported. Differences in as little as one week in gestational age have been shown to be linked to adverse outcomes in infant and child development, including lower scores on Bayley scales of mental and motor development. Gestational age proved to be a strong covariate in several of the Columbia articles. Yet, there is no indication the gestational age was accurately measured and experience shows that it can be off by more than 5 days 40% of the time.
- Nutritional deficiencies such as lack of iodine, vitamin D, vitamin B, and iron or unhealthy diets as well as excessive intake of sugar and fat.
- Exposure to other materials in the environment such as heavy metals and solvents.
- Other issues such as living in settings of violence, drug abuse and other stressors such as maternal stress, bereavement, and depression can also result in decrements in neurodevelopment.
- Conversely, activities as simple as reading aloud have been shown to improve test scores.

Most of these factors were unmeasured in the Columbia study, but are important in understanding the underlying factors of childhood development. These alternate explanations need to be fully considered and accounted for when attempting to establish any causation.

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IV. Brief: Reproducibility is critical for determining scientific validity. *Lack of consistency with other epidemiology studies challenges rather than supports Columbia study findings.*

Background

The US EPA has relied primarily on the Columbia Center for Children's Environmental Health epidemiology study ("Columbia study") to suggest that exposures to chlorpyrifos below the current regulatory endpoint may result in neurodevelopmental effects in infants and children. EPA references papers from two other epidemiology studies (Mt Sinai and CHAMACOS) as also claiming neurodevelopmental outcomes associated with chlorpyrifos and thereby strengthening the validity of the Columbia study claims. Two other studies (HOME and PELAGIE) are also now being cited.

Conclusions

The neurodevelopmental outcomes have been over-generalized across studies. The specific results are not reproduced from the other studies, which challenge the claim of a link between neurodevelopment effects and chlorpyrifos exposures. In fact, the following discussion shows that consideration of the findings *in total across* these studies does not support and even counters such a claim.

Epidemiology studies

The Columbia study relied on measurements of chlorpyrifos, along with other chemicals, in blood at birth from a group of inner city New York City mothers and their children born between 1998 and 2003. The study followed various characteristics in the children later in life, with multiple publications. The Mt Sinai study was also based in New York City, CHAMACOS in California, the HOME study in Ohio, and the PELAGIE study in France. These four studies used urinary metabolites of organophosphate insecticides, potentially including but not limited to chlorpyrifos, to estimate pesticide exposure.

Reproducibility of results is the hallmark of the scientific method

Reproducibility is crucial to giving credence to scientific observations. Even research of the highest quality may have irreproducible findings because of random or systemic error.[1] Since it is impossible to measure and control for all factors that may relate to health effects, epidemiology studies can have false conclusions. There are many examples of specific food items that have been touted as healthy in one study and harmful in another. Scientists, therefore, look for consistency of results in more than one study.

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Consistency is built on the findings for the same exposure and same effect

The definition of consistency across studies has led to controversy. Some claim that any observed health effects from these epidemiology studies support those reported in the Columbia study since they are all *childhood neurodevelopmental effects*. Importantly outcomes like autism, hyperactive behavior and low intelligence, are all very different. Secondly, associations with a class of insecticides do not implicate a specific insecticide, such as chlorpyrifos. The credibility of a true association is in doubt because the epidemiology studies don't link the same exposure and same effect.

As a specific example, all five studies administered an IQ test to the children.[2] The test has several components, such as Working Memory, Verbal Comprehension and Processing Speed, that together make up the overall Full-Scale IQ score. A summary of these publications is shown in the Table.[3-7] Since the Columbia study reported Working Memory and Full-Scale IQ to be inversely associated with chlorpyrifos levels, it makes sense to see if other studies can reproduce this result. Looking crudely at only absolute relationships (direction of scores, i.e. does the score increase or decrease) from left to right across studies, the results do not show consistency. Some scores decrease with increasing exposure levels and other scores increase.

A more robust manner to compare studies is to look for statistical significance. This calculation incorporates the size of the study and strength of the association. Scientists use this calculation to determine the role of chance to say if an association is true or random. As shown below, the Columbia study observed a significant association with chlorpyrifos and Working Memory scores. Mt Sinai and CHAMACOS also reported a decrease in Working Memory scores, but neither found the finding was statistically significant. While CHAMACOS also reported borderline statistical significance for decrease in Full IQ scores, Mt Sinai and HOME studies did not. When considering statistical testing in total across all studies, the other studies *do not* support or replicate the Columbia outcomes.

Conclusion.

The publication by the Columbia University generated the hypothesis that levels of chlorpyrifos in blood at birth were associated with lower IQ and working memory scores in children. Four other studies *have not* consistently reported similar results for *in utero* chlorpyrifos exposure and childhood intelligence.

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Comparison of results for 5 epidemiology studies

Scores	Columbia (age 7)	Mt Sinai (ages 6-9)	CHAMACOS (age 7)	HOME (age 5)	PELAGIE (age 6)
Working memory	Decreased	Decreased	Decreased	Not tested	Increased
Was the finding statistically significant?	Yes	No	No	Not tested	No

	Columbia	Mt Sinai	CHAMACOS	HOME	PELAGIE
Processing speed	Increased	Decreased	Decreased	Not reported	Not reported
Was the finding statistically significant?	No	No	Yes	Not reported	Not reported

	Columbia	Mt Sinai	CHAMACOS	HOME	PELAGIE
Full Scale IQ	Decreased	Decreased	Decreased	Increased	Not reported
Was the finding statistically significant?	Yes	No	Yes*	No	Not reported

*P = 0.08 (not significant) in one analysis and p = 0.05 (statistically significant) in another analysis.

Authors: Carol J. Burns, MPH, PhD, Fellow ACE (Burns Epidemiology Consulting, LLC), George R Oliver, PhD (Dow AgroSciences). June 2018

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