STUDY TITLE
Dow AgroSciences LLC’s Response to EPA’s Revised Human Health Risk Assessment for Chlorpyrifos Registration Review – EPA-HQ-OPP-0850-0224

DATA REQUIREMENTS
None

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STUDY COMPLETED ON
April 29, 2015

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LABORATORY STUDY ID
GRO4302015
STATEMENT OF NO DATA CONFIDENTIALITY CLAIMS

Compound: Chlorpyrifos

Title: Dow AgroSciences LLC's Response to EPA's Preliminary Human Health Risk Assessment for Chlorpyrifos Registration Review – EPA-HQ-OPP-2015-0850-0224

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STATEMENT OF COMPLIANCE WITH GOOD LABORATORY PRACTICE STANDARDS

Title: Dow AgroSciences’ Response to EPA’s Revised Human Health Risk Assessment for Chlorpyrifos Registration Review – EPA-HQ-OPP-2008-0850

Compound: Chlorpyrifos

This report does not meet the definition of a GLP study as it appears in:

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

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

NON-GLP STUDY

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Title: Dow AgroSciences’ Response to EPA’s Revised Human Health Risk Assessment for Chlorpyrifos Registration Review-EPA-HQ-OPP-2008-0850

Report Completion Date: April 29, 2015

NON-GLP STUDY
# TABLE OF CONTENTS

1. EXECUTIVE SUMMARY ........................................................................................................ 10
2. INTRODUCTION .................................................................................................................. 14
   2.1. Overview of Chlorpyrifos Uses and Benefits .......................................................... 14
   2.2. Supported Chlorpyrifos Labels and Uses ............................................................... 15
3. STATUTORY FRAMEWORK .............................................................................................. 16
   3.1. The FQPA Safety Standard ..................................................................................... 16
   3.2. The FQPA Safety Factor ......................................................................................... 17
4. REGULATORY HISTORY REGARDING CHLORPYRIFOS (2000 – PRESENT) .................................................................................................................... 19
   4.1. History of FQPA Safety Factor for Chlorpyrifos .................................................. 21
   4.2. Epidemiology Studies and Their Numerous Limitations and Uncertainties ...... 22
      4.2.1. Limitations and Uncertainties Raised in Preliminary Human Health Risk Assessment and 2008 SAP ................................................................. 23
      4.2.2. Limitations and Uncertainties Raised in 2012 SAP ....................................... 23
      4.2.3. Limitations and Uncertainties Raised in 2012 Federal Peer Review .......... 25
      4.2.4. EPA Recognized that Significant Uncertainties and Limitations Made Use of the Epidemiology Studies Questionable for Risk Assessment Purposes .................................................. 26
   4.3. EPA Repeatedly Sought the Raw Data for the Columbia Study to Determine Whether the Study Could Be Used for Risk Assessment Purposes ................................................................. 27
   4.4. April 15, 2013 Meeting Between EPA and Columbia Researchers Produced None of the Raw Data that EPA Sought ................................................................. 28
   4.5. Notwithstanding the Lack of Raw Data, EPA Relied on the Epidemiology Studies to Increase the PHHRA FQPA Safety Factor from 1X to 10X ........................................... 29
5. EPA’S REVISED HUMAN HEALTH RISK ASSESSMENT HAS SEVERAL SCIENTIFIC AND PROCEDURAL FLAWS, INCLUDING RELIANCE ON THE COLUMBIA STUDY AND THE FAILURE TO CONSIDER CRITICAL DRINKING WATER STUDIES .................................................................................................................... 31
   5.1. The Columbia Study is Replete with Deficiencies that Limit its Scientific Validity, and EPA’s Failure to Address these Deficiencies is Contrary to Agency Policy .................................................................................................................... 31
5.2. EPA’s Failure to Obtain and Review the Raw Data for the Columbia Study Significantly Undermines the Scientific Integrity of the Agency’s Weight-of-the-Evidence Analysis ................................................................. 33

5.3. EPA’s FQPA Safety Factor Determination Contravenes Government Policies of Data Access and Transparency in Scientific Decision-Making ........ 37

5.4. EPA Failed to Provide a Reasonable, Science-Based Explanation for Changing its Preliminary Human Health Risk Assessment Safety Factor Determination of 1X. ........................................................................................... 40

5.5. EPA Failed to Follow Through on Numerous Recommendations that Would Have Added Scientific Clarity to the Columbia Study .................... 42

5.6. Application of the FQPA Safety Factor to EPA’s Occupational Risk Assessment for Chlorpyrifos Is Inappropriate Because the Epidemiology Studies Do Not Provide Adequate Scientific Support ....................... 43

5.7. EPA Failed to Consider Several Critical Studies in its Revised Human Health Risk Assessment ............................................................................. 44

6. EXPERIMENTAL TOXICOLOGY DOES NOT SUPPORT EPA’S USE OF A 10X SAFETY FACTOR ......................................................................................... 47

6.1. Toxicological Basis for Weight of Evidence Assessment Does Not Support Link with Neurodevelopmental Effects ........................................... 48

6.2. Assessment of Experimental Toxicological Studies – Study Design and Lack of Relevance to Humans ............................................................... 48

6.3. Experimental Challenges – Route of Administration, Vehicle Not Relevant to Humans ..................................................................................... 50

6.4. Experimental Dose and Relevance to Humans ................................................................................................................................. 51

6.5. External Reviews of Experimental Toxicology Studies Do Not Support Link Between Neurodevelopmental Effects and Chlorpyrifos Exposure .... 53

6.6. Absence of a Defined Mode of Action/Adverse Outcome Pathway .......... 55

6.7. Recent Studies Show No Toxicological Effect of Chlorpyrifos-Oxon at the Highest Levels that Could Be Found in Drinking Water ................. 57

6.8. Summary .............................................................................................................. 64

7. EPA’S USE OF PBPK MODEL TO CALCULATE DATA-DERIVED EXTRAPOLATION (UNCERTAINTY) (UF) FACTORS (“DDEFs”) WAS APPROPRIATE, BUT SHOULD ALSO BE APPLIED TO PREGNANT WOMEN IN OCCUPATIONAL SETTINGS ................................................. 68

7.1. EPA Appropriately Used the PBPK-PD Model to Derive DDEFs ................. 68

7.2. Dow AgroSciences Has Provided Data to Support Modification of the PBPK-PD Model to Include Gestational Lifestages ....................................... 69
7.3. Comparison of RBC Cholinesterase Inhibition Dose-Response Across Gestational Lifestages. .......................................................................................................................... 70

7.4. DDEF Values in Non-pregnant and Pregnant Human Cohorts Are the Same.................................................................................................................................. 72

7.5. In Utero Exposure/Sensitivity Studies Show No Additional Sensitivity for Fetuses........................................................................................................ 73

8. EPA’S USE OF THE COLUMBIA AND OTHER EPIDEMIOLOGY STUDIES TO BASE ITS RISK ASSESSMENT CONCLUSIONS IS NOT SCIENTIFICALLY SUPPORTED. ................................................................................ 76

8.1. EPA Relies Upon an Unreplicated Study, the Columbia Study. .................. 76

8.2. The Columbia Study has Several Key Limitations which Diminishes its Validity Standing Alone. ........................................................................................................ 77

8.2.1. The Analytical Method Used in the Columbia Study Has Not Been Validated at the Low Concentrations Reported in the Blood. ......................... 77

8.2.2. There are Credible Alternative Explanations for the Neurodevelopmental Effects Observed in the Columbia Study. ............... 78

8.2.3. Measurements in the Columbia Study Do Not Reflect Exposure Over Time. ............................................................................... 80

8.2.4. Adverse Results Reported in the Colombia Study Are Not Found in Other Populations. ................................................................. 80

8.3. EPA’s Weight of Evidence Analysis is Poorly Executed and is Characterized by Accumulating a List of Positive Findings in the Absence of a Mode of Action. ...................................................................................... 81

8.4. All Epidemiology Studies Relied Upon by EPA Are Marked by a Lack of Transparency and No Underlying Raw Data. .................................................. 84

8.5. There is No Standard or Process Used to Insure Transparency and Validation of the Epidemiology Study Results....................................................... 85

8.6. Decision-Making Regarding Epidemiology is Qualitative and Lacks Scientific Rigor. ........................................................................................... 85

8.7. The Epidemiology Study Results are Based on Outdated Use Patterns From More Than Fifteen Years Ago. ......................................................... 86

8.8. In Conclusion, the Epidemiology Data are Not Sufficiently Robust to Support the Hypothesis that Chlorpyrifos is a Causal Factor in Neurodevelopmental Effects...................................................................................... 87

9. OCCUPATIONAL MIXER/LOADER/APPLICATOR/FLAGGER FOR CROPS, NON-CROPS AND SEEDS & REI ................................................................. 92

9.1. Occupational Risk Assessment Safety and Uncertainty Factors Should Result in LOC of 4................................................................................... 92
9.2 Occupational Handler Exposure Assessment: Overall Comment; Opportunities for Refinement ................................................................. 93
9.3. Unit Exposures for Occupational Exposure Assessment .......................................................... 94
9.4. Restricted Entry Intervals - Hand Harvesting Activities ......................................................... 95
9.5. Transfer Coefficients for Cabbage and Dormant or Delayed Dormant Tree Fruit .......................................................... 96
9.6. Level of Concern for Re-Entry Exposures ........................................................................... 96
9.7. Refinement of Assessment for Seed Treatments ................................................................. 96
9.8. PPE for Airblast Applications ......................................................................................... 97
9.9. Additional Refinement for Aerial Application ................................................................. 97

10. THERE ARE NO BYSTANDER EXPOSURE RISKS ......................................................... 99
10.1. Recent Studies Show that Volatilization of Chlorpyrifos is Not a Risk ......................... 99
10.2. Based on the PBPK Model, Current Spray Drift Buffers Are Overly Conservative and Should Be Revised .............................................. 99

11. DOW AGROSCIENCES CONCURS THAT THE REFINED DIETARY EXPOSURE ASSESSMENT OF CHLORPYRIFOS RESULTS IN ACUTE AND STEADY STATE FOOD-ONLY EXPOSURES THAT ARE SIGNIFICANTLY LESS THAN THE LEVEL OF CONCERN TO HUMANS .................................................. 101
11.1. Dietary Risk Assessment (food only) Well Below aPAD and cPAD ......................... 101
11.2. Aggregate Risk Estimates ............................................................................................ 102
11.3. Acute Dietary (Food Only) Risk Assessment – Impact of 10X Intraspecies UF for Females (13-49 years old) ................................................................. 102
11.4. Acute Dietary (Food Only) Risk Assessment – Impact of 10X FQPA UF for Females (13-49 years old) ........................................................................ 103
11.5. Steady State Dietary (Food Only) Risk Assessment – Impact of 10X Intraspecies UF for Females (13-49 years old) .................................................. 104
11.6 Steady State Dietary (Food Only) Risk Assessment - Impact of 10X FQPA UF for Females (13-49 years) ........................................................................ 104

12. DIETARY (DRINKING WATER) .................................................................................... 106
12.1. Introduction .............................................................................................................. 107
12.2. EPA Failed to Consider a Report Previously Submitted to the Agency Demonstrating No Risk from Exposure to Chlorpyrifos-oxon in Drinking Water .......................................................................................... 108
12.3. EPA Failed to Consider Previously Submitted Comments and Reports Providing Drinking Water Estimates Based on Monitoring .......... 109
12.4. Comments on Specific Sections of the EFED Document ........................................... 110
12.5. Conclusion and Recommended EDWC ............................................................. 124

13. RESIDUES/TOLERANCE .......................................................................................... 128

13.1. Comments on Specific Sections of 2.0. HED Recommendations; 2.1 Data
      Deficiencies; Residue Chemistry ....................................................................... 128

13.2. Comments on Specific Sections of 2.1. Tolerance Considerations; 2.2.3
      Recommended/Reassessed Tolerances .............................................................. 130
1. EXECUTIVE SUMMARY

Dow AgroSciences, LLC (“DAS”) respectfully submits these comments on the Chlorpyrifos Revised Human Health Risk Assessment (“RHHRA”) completed by the U.S. Environmental Protection Agency (“EPA” or “Agency”) in December 2014. Chlorpyrifos is one of the most widely used agricultural insect control products in the world. Chlorpyrifos has played a key role in pest management efforts in the U.S. and around the world for more than 50 years and is currently used to protect a number of critical U.S. food crops from depletion due to insect pests.

In 2006, EPA completed a Reregistration Eligibility Decision for chlorpyrifos, finding that existing registrations were eligible for reregistration under the Federal Insecticide, Fungicide, and Rodenticide Act (“FIFRA”) and that any potential exposures to infants and children were safe under the Federal Food, Drug, and Cosmetic Act (“FFDCA”), as amended by the Food Quality Protection Act of 1996 (“FQPA”). In 2007, a petition was filed with the Agency challenging the registration of chlorpyrifos because, inter alia, EPA had not quantitatively considered in its risk assessment for the Reregistration Eligibility Decision certain epidemiology studies. EPA had never before included epidemiology studies quantitatively in a pesticide risk assessment because epidemiology studies traditionally have been neither sufficiently robust nor reliable for risk assessment decision-making. Nevertheless, EPA accelerated its registration review of chlorpyrifos in order to respond to the petition’s challenges.

In 2011, with published articles regarding the epidemiology studies and a review of those studies by a Scientific Advisory Panel (“SAP”) in hand, the Agency stated, in its Preliminary Human Health Risk Assessment (“PHHRA”), that it had an “extensive” toxicological data set which supported registration review and an FQPA safety factor of 1X. Subsequent to that statement, EPA undertook further review of the epidemiology studies and also received additional information from DAS including vapor phase inhalation studies, pharmacokinetic (PBPK) models and results, and a chlorpyrifos-oxon toxicity study in drinking water. A study involving modeling of drinking water exposures and comparison to biomonitoring data was also provided to the Agency. Inexplicably, in its 2014 revised risk assessment, EPA essentially ignored both its prior preliminary FQPA safety factor determination of 1X and the increased robustness of its already extensive data set, and instead relied on the same epidemiology studies to increase the preliminary FQPA safety factor to 10X. The Agency similarly ignored the additional critical drinking water data.

DAS supports a rigorous, science-based, and transparent regulatory process for assessing the potential human health risk of chlorpyrifos; FIFRA, FFDCA and FQPA demand no less. The Agency has described its effort to integrate epidemiology into risk assessment in response to the petition as one that...
will “lead the way” for subsequent pesticide assessments, but also one involving “novel scientific questions” “with a steep learning curve” on the “frontiers of science.”¹ Thus, it is all the more important for EPA to carefully and fully address the scientific issues that relate to this risk assessment. Unfortunately, EPA’s RHHRA looks in many respects more like a rush to judgment that is not well-grounded in either science or law.

As set forth herein, DAS is deeply concerned with the Agency’s precedent-setting reliance on the reported results of a single epidemiology study – the Columbia Study – for which the Agency lacks underlying data, to support an increase in the preliminary FQPA safety factor for chlorpyrifos from 1X to 10X. EPA’s reliance on this unreplicated study—to the exclusion of a complete database of toxicological studies and in the absence of supporting raw data—lacks scientific rigor, ignores EPA’s statutory obligation to base safety factor determinations on reliable data, and contravenes the Agency’s policies of data access and transparency in scientific decision-making.

DAS is concerned that EPA’s continued reliance on the Columbia Study will lower the standard for scientific rigor in regulatory decision-making and significantly reduce the continued availability and use of chlorpyrifos in U.S. agriculture. The Columbia Study is rife with limitations and uncertainties that diminish its scientific validity. In particular, and to name just a few: (1) adverse outcomes reported in the Columbia Study are not generalizable to the broader population and there are questions about the analytical method and its accuracy when used to measure chlorpyrifos exposure; (2) the study’s small sample size generates instability in its use; and (3) the study does not establish a biologically plausible mode of action. The 2008 Scientific Advisory Panel (“SAP”), 2012 SAP, and 2012 Federal Peer Review made several recommendations to EPA aimed at addressing the study’s shortcomings that the RHHRA fails to adequately address or even consider.

Even more troubling is the Agency’s reliance on the Columbia Study to increase the FQPA safety factor while lacking access to the underlying data that allegedly support the study’s conclusions—data for which EPA has publicly expressed frustration at its inability to obtain and that the Agency has acknowledged are necessary to thoroughly assess the Columbia Study’s conclusions concerning potential health risks associated with chlorpyrifos. Although the Columbia Study was supported by federal funds, EPA’s requests for the data set underlying the Columbia Study were rebuffed by the Columbia researchers. Instead, EPA held a meeting with the Columbia researchers to discuss the Agency’s questions about the data. No meeting minutes, notes, or transcripts from this meeting have been made

publicly available. Following this closed-door meeting, in which EPA learned of additional significant limitations and uncertainties with the Columbia Study, EPA appears to have abandoned its efforts to obtain the raw database on their statements in the RHHRA, and yet EPA still relies on the results reported for the Columbia Study to justify a tenfold increase in the preliminary FQPA safety factor for chlorpyrifos. EPA made this determination despite a complete database of contradictory toxicological data that its earlier 2011 Preliminary Human Health Risk Assessment (“PHHRA”) had concluded were supportive of a 1X FQPA safety factor for chlorpyrifos.

EPA’s reliance on the Columbia Study in the absence of a full review of supporting data vitiates EPA’s statutory mandate under the FQPA, which requires safety factor determinations to be based on complete and reliable data. In addition, EPA’s own guidance for the use of epidemiological studies in risk assessments requires that epidemiology studies, whether used quantitatively or qualitatively, represent the best available data. EPA’s reliance for a pesticide safety factor determination on an epidemiology study for which the Agency lacks confirmatory data sets a dangerous precedent for future pesticide risk assessment decisions. In short, Congress never intended FQPA’s safety factor to be based on the uncertainty caused by EPA’s own failure to obtain and review the underlying data for a study that the Agency has allowed to drive its risk assessment.

EPA’s precedent-setting action with respect to chlorpyrifos also flouts the Administration’s stated policies of data access and transparency in scientific decision-making. Official directives issued by President Obama, Office of Science and Technology Policy Director John Holdren, and former EPA Administrator Jackson all repeat the same refrain: regulatory decisions must be based on sound, reliable, and publicly available scientific information. DAS is particularly concerned that the Agency’s basing a significant regulatory decision on an epidemiology study for which it lacks supporting data creates a double standard for academic researchers and members of the regulated community, who are subject to strict regulations requiring the availability and disclosure of raw data supporting studies submitted to obtain or maintain pesticide registrations.

As also discussed herein, the limitations and other flaws that undermine EPA’s use of epidemiology to support a 10X safety factor also undermine the Agency’s reliance on epidemiology studies to extend the safety factor to occupational scenarios.

EPA’s use of experimental toxicological studies to form the basis for its proposed linkage between chlorpyrifos and neurodevelopmental effects is also of concern. These studies have significant methodological and design challenges that severely limit their utility in a weight-of-evidence assessment. For example, many of these experimental studies use dose levels that are tens of thousands of times higher than actual human exposures and thus these studies are of questionable applicability when
assessing potential risk to humans. There is no compelling scientific (animal or human) evidence or a proposed, tested, and validated mode of action to support either the contention that chlorpyrifos is associated with neurodevelopmental effects in humans or that there is a sound basis for a 10X FQPA safety factor.

On the other hand, DAS commends the Agency for its reliance on cutting-edge physiologically based pharmacokinetic (“PBPK”) modeling to develop data-derived extrapolation factors (“DDEFs”) for chlorpyrifos. DAS has addressed the Agency’s comments regarding using the PBPK modeling to develop DDEF values for pregnant workers with updates to the PBPK/PD model and urges EPA to accept the new modeling. The reduction in the FQPA safety factor to 1X and the use of an intraspecies uncertainty factor of 4X for all population groups, including women during pregnancy, based on the additional PBPK modeling discussed in this document, would have a significant impact on the outcome of the Occupational Risk Assessment in the RHHRA. With these changes, the Level of Concern (“LOC”) would be reduced to 4, and all current occupational use scenarios would meet the acceptable risk standard with the requirements for personal protective equipment/engineering controls (“PPE/EC”), use rates, and Re-entry Intervals (“REI”) on current DAS labels.

In addition, as noted above, EPA’s failure to consider several important studies submitted in forming its conclusions concerning potential health risks associated with chlorpyrifos presents grave concerns as they call into question such conclusions and whether EPA has met its mandate. The first study is a toxicological study that demonstrates no risk from exposure to chlorpyrifos-oxon in drinking water. In this study, no hazard was found at doses 7-times the level of chlorpyrifos that could actually be found in drinking water based on the water solubility of chlorpyrifos. Aligned with the principle EPA used in the decision of no risk from potential volatilization, no hazard therefore equates to no risk from potential exposures through drinking water. In the second study, based on 47,000 water samples from available water monitoring surveys of community water systems on both large to small rivers and streams taken during various time periods between 1991 and 2013, statistical methods allowed the characterization of the distribution of exposures at the higher percentiles of exposure. Exposures dropped to only slightly above 10% of both the acute and chronic levels of concerns. The results matched well with exposures based on Centers for Disease Control (“CDC”) biomonitoring data. These drinking water studies were submitted in June and August of 2014, respectively, but the RHHRA failed to even mention either study. EPA’s failure to consider the oxon study was particularly baffling in view of the fact that EPA provided comments on the study design and participated in a discussion of the study’s results. EPA also failed to cite in its RHHRA several comprehensive reviews on chlorpyrifos (Eaton et al. 2008; Li et al. 2012; Prueitt et al. 2012), which yield perspective on neurodevelopmental effects in experimental
studies, exposure, and weight of evidence frameworks. That the RHHRA does not address these important studies, generated at great expense to the registrant, raises further questions as to whether EPA has met its obligation to ensure that regulatory decisions are based on reliable and inclusive scientific data.

DAS appreciates the Agency’s consideration of the numerous scientific, policy and legal-based concerns set forth herein, as well as those expressed in the separate submissions of Exponent Inc., Gradient®, and RTI International, which are incorporated herein by reference. These concerns must be addressed in a transparent, scientifically robust manner now so that confidence in the Agency’s registration process is not undermined. The attached comments provide further detail on these key issues. In Sections 2-6, these comments focus on regulatory history with respect to chlorpyrifos and legal, policy and regulatory issues raised by the RHHRA. Sections 6-13 provide the scientific analysis and support for the positions set forth in these comments.

2. INTRODUCTION

2.1. Overview of Chlorpyrifos Uses and Benefits

Chlorpyrifos is a broad-spectrum organophosphate (“OP”) insecticide used to control a variety of insects. Chlorpyrifos was first registered for use in the U.S. during 1965 and the first crop use was approved in 1974. It has served an important role in pest management efforts supporting a safe and abundant food supply for nearly 40 years.

Chlorpyrifos is currently one of the most widely used insecticide products in agriculture in the U.S. and around the world. In the U.S., chlorpyrifos products protect a number of important agricultural crops, such as soybeans, wheat, alfalfa, citrus, tree nuts, peanuts, vegetables, and many minor crops, from losses due to insect pests. Permanent food safety tolerances have been established by EPA for the residues of chlorpyrifos in or on a variety of agricultural crops and commodities, including meat, milk, poultry and eggs. See EPA’s Chlorpyrifos: Preliminary Human Health Risk Assessment for Registration (“PHHRA”) at 7 (June 30, 2011). DAS completed and previously posted to the Federal Docket (EPA-HQ-OPP-2008-0850-0016) a report entitled: Use and Benefits of Chlorpyrifos in U.S. Agriculture (Gomez, 2010, which remains an accurate outline of the importance of chlorpyrifos and describes its role in agriculture including discussion of regional, crop and pest-specific use information.
2.2. **Supported Chlorpyrifos Labels and Uses**

As the primary chlorpyrifos technical product registrant and data owner, DAS confirms that the Company supports support is limited to only the current agricultural uses of chlorpyrifos as described on DAS product labels. Thus, DAS supports the use of chlorpyrifos on food crops, including fruit and nut trees, many types of fruits and vegetables, grain crops; select non-crop uses such as sod farms, and commercial seed treatment only.

**Section 2 References**


3. STATUTORY FRAMEWORK

EPA regulates pesticides under FIFRA and the FFDCA. In order for EPA to register, or maintain
the registration of, a pesticide under FIFRA, the scientific data and other information must show that use
of the pesticide “will not generally cause unreasonable adverse effects on the environment.” FIFRA §
3(c)(5)(D), 7 U.S.C. § 136a(c)(5)(D). Since 1996, FIFRA has defined “unreasonable adverse effects on
the environment” as

(1) any unreasonable risk to man or the environment, taking into account the economic,
    social, and environmental costs and benefits of the use of any pesticide, or (2) a human
dietary risk from residues that result from a use of a pesticide in or on any food
inconsistent with the standard under [FFDCA] section 346a . . . .


With respect to the human dietary risk component of FIFRA’s definition of “unreasonable
adverse effects on the environment,” section 408 of the FFDCA, 21 U.S.C. § 346a, requires EPA to set
“tolerances” for the maximum levels of pesticide chemical residues allowed in or on food. Without such
a tolerance (or exemption from a tolerance), food containing a pesticide chemical residue is “adulterated”
under the FFDCA and may not be moved in interstate commerce. 21 U.S.C. §§ 331, 342(a)(2)(B). The
same is true for residues that exceed an established tolerance level. Id. In considering whether to
establish, modify, or revoke a tolerance (or exemption from a tolerance), EPA must consider, among
other relevant factors, “the validity, completeness, and reliability of the available data from studies of the
pesticide chemical and pesticide chemical residue.” FFDCA § 408a(b)(2)(D)(i), § 346a(b)(2)(D)(i)
(emphasis added).

3.1. The FQPA Safety Standard

The Food Quality Protection Act of 1996 amended both FIFRA and FFDCA. In particular,
FQPA established a single health-based safety standard (the “reasonable certainty of no harm” standard)
under section 408 of FFDCA for all pesticide residues in or on food. § 408(b)(2)(A)(ii), 21 U.S.C. §
346a(b)(2)(A)(ii); 1996 Food Quality Protection Act – Implementation Plan, USEPA, Mar. 1997, at 11,

Pesticides; Guidance on Pesticide Import Tolerances and Residue Data for Imported Food; Request for
Comment, 65 Fed. Reg. 35,069, 35,071. Specifically, EPA may establish a tolerance for a pesticide if
EPA determines that the tolerance is “safe,” and must modify or revoke a tolerance if EPA determines
that the tolerance is not “safe.” § 408(b)(2)(A)(i), 21 U.S.C. § 346a(b)(2)(A)(i). A tolerance is deemed
“safe” under the FFDCA if EPA has concluded 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.*” § 408(b)(2)(A)(ii), 21 U.S.C. § 346a(b)(2)(A)(ii) (emphasis added). While this safety standard was new to EPA, the same standard has been used for decades by the Food and Drug Administration (FDA) for food additives based on the legislative history of the 1958 Food Additives Amendment. See H.R. Rep. No. 2284, 85 Cong. 2d Sess. 4 (1958); S. Rep. No. 2422, 85 Cong., 2d Sess. 6 (1958); 21 C.F.R. § 170.3(i) (1977). FQPA also revised the registration test for a food use pesticide under FIFRA to expressly include a human dietary risk component, as noted above, based on the FQPA safety standard of reasonable certainty of no harm. See FIFRA § 2(bb)(2), 7 U.S.C. § 136(bb)(2).

An assessment of aggregate exposure to the pesticide chemical residue is a critical component of the FQPA safety standard. In practice, this provision requires EPA to assess the aggregate exposure levels of consumers, including infants and children, to the pesticide chemical residue, adding together exposure from any proposed new food use, all existing food uses, and other non-occupational sources, which EPA has interpreted to include exposure from drinking water and residential uses, indoor and outdoor. 21 U.S.C. §§ 346a(b)(2)(D)(v) and (vi); 1996 Food Quality Protection Act – Implementation Plan, USEPA, Mar. 1997, http://www.epa.gov/pesticides/regulating/laws/fqpa/impplan.pdf.

Taken together, the amendments made to FFDCA and FIFRA by FQPA in 1996 require a pesticide to meet the FQPA safety standard in order to have a tolerance (or exemption from tolerance) and be registered for a food use. And, to the extent there was any doubt, Congress expressly applied the same FQPA safety standard to infants and children. Specifically, Section 408(b)(2)(C) provides that when EPA establishes, modifies, leaves in effect, or revokes a tolerance or exemption, the Agency must “ensure that there is a reasonable certainty that no harm will result to infants and children from aggregate exposure to the pesticide chemical residue.” § 408(b)(2)(C)(ii)(I), 21 U.S.C. § 346a(b)(2)(C)(ii)(I).

3.2. The FQPA Safety Factor

In making determinations of health risk, EPA often applies a safety factor for inter-species variability (to account for the applicability of animal data to humans), and an additional safety factor for intra-species variability (to account for variability of toxicity responses in humans). In an effort to be responsive to the report, “Pesticides in the Diets of Infants and Children,” issued by the National Research Council (“NRC”) in 1993, the FQPA required that, when applying the FQPA safety standard to infants and children, EPA must apply an additional tenfold margin of safety “to take into account potential pre- and post-natal toxicity and completeness of the data with respect to exposure and toxicity to infants and children,” unless, based on “*reliable data,*” EPA determines that a lower safety margin will be safe for infants and children. § 408(b)(2)(C)(ii), 21 U.S.C. § 346a(b)(2)(C)(ii)(I) (emphasis added); H.R. Rep. No.
This provision regarding the additional safety margin for infants and children in FFDCA § 408(b)(2)(C) is often referred to as the “FQPA safety factor”, “FQPA uncertainty factor” or “tenfold safety factor.” EPA has discretion to “use a different margin of safety for the pesticide chemical residue only if, on the basis of reliable data, such margin will be safe for infants and children.” Id. Thus, “reliability” of scientific data is the cornerstone of EPA’s determination with respect to whether a pesticide tolerance is “safe” for infants and children.

The FFDCA does not define “reliability” or “reliable data.” However, in a February 2002 guidance document addressed to risk assessors in the Office of Pesticide Programs (“OPP”), EPA counseled that “the data and information that form the basis for the selection of a different safety factor [for infants and children] must be sufficiently sound such that OPP could routinely rely on such information in taking regulatory action.” EPA, Determination of the Appropriate FQPA Safety Factor(s) in Tolerance, at A-6 (Feb. 28, 2002) (“EPA Safety Factor Guidance”). The guidance further states that “it is critical to the protection of infants and children that [OPP] does not rely on a default value or presumption in making decisions under Section 408 where reliable data are available that support an individualized determination.” Id. at 12.

In addition to its obligation under FFDCA to ensure that tolerance decisions are informed by “reliable data,” EPA has an obligation under FIFRA to ensure that any public review to develop a risk-benefit evaluation of a pesticide or any of its uses must be “based on a validated test or other significant evidence raising prudent concerns of unreasonable adverse risk to man or the environment,” an obligation that exists “[n]otwithstanding any other provision of [FIFRA]”. FIFRA § 3(c)(8), 7 U.S.C. § 136a(c)(8).
In June 2000, as part of the reregistration process for chlorpyrifos, EPA released a revised human health risk assessment. PHHRA at 2. In conjunction with that action, the technical registrants of chlorpyrifos voluntarily cancelled and phased out certain of its uses. According to EPA, the “voluntary cancellation/phase out expeditiously addressed the food, drinking water, residential and non-residential uses posing the greatest risks estimated for children.” PHHRA at 2. Risk mitigation measures included cancellation of all homeowner use product registrations (except for insect bait stations). PHHRA at 2.

In February 2002, EPA issued an Interim Reregistration Eligibility Decision (“IRED”) for chlorpyrifos. The IRED required additional mitigation measures addressing occupational and ecological risks, including reduced application rates and seasonal maximum limits, increased retreatment intervals and increased personal protective equipment and/or engineering controls. “With that mitigation in place, EPA found the exposures to chlorpyrifos were consistent with both FIFRA and FFDCA standards.” Decl. of Jack Housenger in Supp. of Opp’n to Pet. for a Writ of Mandamus (“Housenger Decl.”) ¶ 9, In re Pesticide Action Network N. Am. v. U.S. EPA, No. 12-71125 (9th Cir. July 24, 2012), ECF No. 9-2 at 6.

EPA also conducted a cumulative risk assessment that evaluated the combined human dietary and non-occupational exposures to all of the OPs because all OPs share a common mechanism of toxicity – AChE inhibition. In 2006, EPA determined that these cumulative exposures were also safe. Housenger Decl. ¶ 9. “Importantly, in both the aggregate assessment and the [cumulative risk assessment], EPA also concluded that exposures to infants and children were safe, taking into account the special emphasis that the FFDCA places on ensuring that EPA’s decisions are protective for these early life stages.” Housenger Decl. ¶ 9. At the same time, “EPA announced that it had also completed its FIFRA reregistration eligibility determination for chlorpyrifos, finding that existing registrations were eligible for reregistration under the FIFRA ‘no unreasonable adverse effects’ standard.” Housenger Decl. ¶ 9. The IRED for chlorpyrifos became final (as a Reregistration Eligibility Decision) in July 2006. PHHRA at 2.

In September 2007, Pesticide Action Network North America and the Natural Resources Defense Council (collectively “Petitioners”) submitted a petition to EPA seeking the revocation of all FFDCA food safety tolerances for chlorpyrifos and the cancellation of all chlorpyrifos pesticide product registrations under FIFRA. Petition to Revoke All Tolerances and Cancel All Registrations for the Pesticide Chlorpyrifos (Sept. 12, 2007) (“PANNA Petition”). “That petition was in large measure styled as a challenge to the safety findings regarding human health that EPA had made in reregistering chlorpyrifos and maintaining the chlorpyrifos tolerances in connection with tolerance reassessment under FFDCA section 408(q).” Housenger Decl. ¶ 10. Petitioners raised several claims, including that EPA had failed to quantitatively incorporate certain epidemiology studies (discussed below) in its risk
assessment and had failed to apply an appropriate safety factor for children pursuant to the Food Quality Protection Act. See PANNA Petition at 5–6, 10–11. The Petition subsequently ended up in court. Pet. For Writ of Mandamus, In re Pesticide Action Network N. Am., No. 12-71125 (9th Cir. April 12, 2012), ECF No. 1.

In response to the Petition, EPA determined that further study was needed regarding OPs, and chlorpyrifos in particular. Housenger Decl. ¶ 13. Accordingly, “EPA decided that it was appropriate to move up the registration review of chlorpyrifos in order to complete that review several years in advance” of 2022 – the next registration review deadline for chlorpyrifos under FIFRA Section 3(g). Id. To that end, in September 2008, EPA convened a FIFRA SAP to provide a preliminary review of experimental toxicology and epidemiology data available at that time, including studies by Columbia University and Mt. Sinai School of Medicine researchers regarding the effects of chlorpyrifos on birth outcomes and child development. Housenger Decl. ¶ 14. These epidemiology studies are further discussed below.

“In order for EPA to consider incorporating the chlorpyrifos epidemiologic data into the chlorpyrifos risk assessment [for the registration review], EPA first had to establish a framework for undertaking such an effort in a transparent and rigorous manner.” Housenger Decl. ¶ 16. Thus, in February 2010, EPA convened an SAP to review the Agency’s draft “Framework for Incorporating Human Epidemiologic & Incident Data in Health Risk Assessment,” which, according to the Agency, “provides the conceptual foundation for evaluating and integrating multiple lines of scientific evidence in a human health risk assessment.” Id.

EPA has said that its efforts to respond to the demands set forth in PANNA’s Petition by incorporating epidemiology into pesticide risk assessment involve the precedent-setting use of novel science:

[M]any of the analyses we are conducting on chlorpyrifos in order to address [PANNA’s] Petition . . . involve issues on the cutting edge of science that have often required the development of new methodologies. EPA’s chlorpyrifos assessment is essentially leading the way for the subsequent assessments EPA will be conducting on other pesticides in the FIFRA registration review process and it comes with a steep learning curve, as is often the case in addressing novel scientific questions.

Vogel Decl. ¶ 5. During the summer of 2011, EPA released for public comment its PHHRA for chlorpyrifos as part of its registration review process. Subsequent to the PHHRA, in April 2012, EPA convened an SAP to review the Agency’s preliminary conclusions regarding a “weight-of-evidence” evaluation integrating the epidemiologic data with the experimental toxicology studies for the neurodevelopmental outcomes and AChE inhibition. Housenger Decl. ¶ 18. On July 12, EPA received the report of the April 2012 SAP. Housenger Decl. ¶ 19.
Finally, in 2012 EPA sought input from scientists within the federal government regarding a 2012 epidemiology study describing the results of magnetic resonance imaging on a subset of the children in the Columbia Study. (“2012 Federal Peer Review”). See January 25, 2013 letter from Steven Bradbury, Ph.D., Director, Office of Pesticide Programs, U.S. EPA at 4 (“Bradbury letter”). As part of the 2012 Federal Peer Review, EPA also sought input in areas of neuro and motor development in children outside of the expertise of the SAP. Bradbury letter at 4. The 2008 SAP, 2012 SAP, and 2012 Federal Peer Review are discussed in more detail below.

4.1. History of FQPA Safety Factor for Chlorpyrifos

EPA’s human health risk assessment for chlorpyrifos issued in 2000 was largely based on adult laboratory animal data for cholinesterase inhibition, and used the 10X FQPA safety factor. PHHRA at 2. Subsequent to 2000, there was “extensive and ongoing research on various aspects of chlorpyrifos including its neurological effects in \textit{in vitro} and in animals and humans following gestational and post-natal exposures, and its pharmacokinetics.” PHHRA at 2. In 2008, EPA developed a draft issue paper that reviewed the available science for chlorpyrifos. PHHRA at 2. That paper was reviewed by an SAP in 2008. PHHRA at 2. Subsequent to the SAP review, new studies were submitted to EPA, including a special acute inhibition study, an immunotoxicity study, and acute and repeat dose comparative cholinesterase assays in juvenile and adult rats. PHHRA at 2. The latter studies examined toxicity for both chlorpyrifos and its metabolite – chlorpyrifos oxon. PHHRA at 2, 40.

EPA’s PHHRA for chlorpyrifos, dated June 30, 2011, reviewed “existing data, findings of new studies made available since the 2000 assessment, and consider[ed] comments from the 2008 SAP review.” PHHRA at 2. In the PHHRA, the Agency stated that the “toxicological database for chlorpyrifos is extensive and is adequate to support the registration review.” PHHRA at 36 (citation omitted). In addition, the Agency found “no residual uncertainties in the exposure database.” PHHRA at 40. Also, according to EPA, “the dietary risk assessment is conservative and is not expected to underestimate dietary exposure to chlorpyrifos and chlorpyrifos oxon.” PHHRA at 40. Accordingly, the Agency determined that:

Similar to risk assessments conducted for other ChE-inhibiting pesticides where juvenile pups provide the PoDs for risk assessment, the FQPA SF is being reduced to 1X for this preliminary assessment for acute and chronic oral exposure, in addition to dermal and inhalation exposure to chlorpyrifos . . . . For chlorpyrifos oxon, the Agency proposes to reduce the FQPA SF to a 1X for acute and chronic exposure . . . .
The Agency also stated that “[i]n those instances where the Agency has proposed to reduce the FQPA SF to 1X, the Agency believes data are supportive of this proposal.” PHHRA at 36. (emphasis added). EPA noted that it was conducting on-going analysis of published literature studies on a variety of challenging scientific issues such as “interpretation of epidemiology studies in the context of assessing human health risk to chlorpyrifos.” Id. Therefore, the “PoDs proposed in this preliminary assessment, and associated uncertainty FQPA factors, could change.” PHHRA at 39. As discussed below, in its 2014 revised risk assessment, EPA determined on the basis of certain epidemiology studies that the FQPA safety factor should be increased from 1X to 10X. RHHRA at 49.

4.2. Epidemiology Studies and Their Numerous Limitations and Uncertainties

As part of its PHHRA, EPA noted the existence of three epidemiology cohort studies with multiple publications for each, funded by multiple federal agencies that attempted to evaluate pre- and post-natal pesticide exposure to chlorpyrifos or other OPs. PHHRA at 29-34. The studies originated from: (i) Columbia University’s Center for Children’s Health (research program referred to as the “Columbia Study” (with multiple papers research papers including Whyatt 2005 and Rauh et al. 2006, 2011)), (ii) Mt. Sinai School of Medicine (with multiple papers including Berkowitz et al. 2004 and Engel et al. 2007, 2011) (“Mt. Sinai Study”); and, (iii) University of California at Berkeley (Center for Health Assessment of Mothers and Children of Salinas (with multiple papers including Eskenazi et al. 2004, 2007, HUEN ET AL., 2012, Bouchard et al. 2011) (“CHAMACOS Study”). PHHRA at 30. “The first two study populations include multi-ethnic, urban low income mother-infant pairs, and the latter reflects a farm worker/agricultural worker study population.” Id. The Columbia Study focused on measurement of chlorpyrifos in maternal cord blood while the Mt. Sinai study and the CHAMAOS study assessed non-specific organophosphate metabolites in maternal urine. Id.

2 For acute inhalation exposure, the PHHRA retained a “10X FQPA database uncertainty factor” “to account for LOAEL to NOAEL extrapolation.” PHHRA at 41.
4.2.1. Limitations and Uncertainties Raised in Preliminary Human Health Risk Assessment and 2008 SAP

EPA’s 2011 PHHRA considered the above-referenced epidemiology studies, as well as the 2008 SAP review of them, and noted numerous uncertainties and other limitations with respect to the studies, including the following:

- “All three cohort studies have limitations that include multiple chemical exposures and exposure to other organophosphates.” PHHRA at 32.
- “[T]he SAP also noted that it cannot be stated that chlorpyrifos is the sole contributor to the observed outcomes; exposures to all three ACh-E inhibiting insecticides may act in combination to produce the observed effects.” PHHRA at 32; 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 (“2008 SAP Minutes”) at 37.
- “While neurodevelopment deficits may be multifactor in origins [the children in these studies] are from low income multi-ethnic populations and urban neighborhoods and may experience other exposures that may also influence neurodevelopmental outcomes.” PHHRA at 33.
- “Challenges in the interpretation of the Mt. Sinai and [CHAMACOS] studies include use of non-specific measures of pesticide exposure, based on OP and carbamate metabolites, rather than chlorpyrifos, reduce their utility in a quantitative context for the chlorpyrifos risk assessment.” PHHRA at 33.
- “The SAP recommended [in 2008] that the epidemiology . . . should not be considered quantitatively for PoDs . . . .” PHHRA at 33.

EPA stated that it would “carefully consider the strengths and limitations of the epidemiology studies along with the available empirical data in a full weight of evidence analysis in the final [human health risk] assessment.” PHHRA at 34 (emphasis added). In the meantime, however, the Agency believed, as noted above, that its database supported reducing the FQPA safety factor from 10X to 1X. PHHRA at 36.

4.2.2. Limitations and Uncertainties Raised in 2012 SAP

The 2012 SAP also noted several limitations and other concerns with respect to the epidemiology studies, including the following:

- “[T]he studies entail a multi-chemical exposure spanning a multi-year period that encompasses an important period of sequential developmental processes necessary for brain maturation. Thus,
panel members caution that it is very difficult to attribute the independent physiological effects to
a single chemical in this type of multi-chemical exposure scenario. . . [I]t cannot be stated that
chlorpyrifos is the sole contributor to the observed outcomes.” 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 17, 45 (July 11, 2012).

- “An additional concern raised by the Panel is the modest sample sizes of the studies. [The Panel]
deem[s] inadequate sample size as one of the most important limitations of these studies.” 2012
SAP Minutes at 17-18.
- “As a result, it cannot be concluded that chlorpyrifos is the only contributor to the observed
outcomes.” 2012 SAP Minutes at 18.
- “The Panel recognizes the limitations of estimating chlorpyrifos exposures based on the exposure
measures collected in the three longitudinal children’s cohort studies (i.e., the Columbia Study,
the Mt. Sinai study, and the CHAMACOS study). Consequently, the Panel largely concurs with
EPA that the data generated from these studies alone are not adequate enough to obtain a point of
departure (POD) for the purposes of quantitative risk assessment. . . [T]he use by the three
studies of different exposure matrices . . . and different targeted analyses . . . make the effort of
deriving a definitive POD based on those data alone impossible.” 2012 SAP Minutes at 19, 50
(emphasis added).

- “Maturation of the brain is a critically timed sequence of events with each subsequent event
dependent upon the successful completion of the previous one. Thus, appropriate brain function
at age 7 is dependent on completion of maturation processes that occur at earlier ages. . . . [T]his
brain maturation process would need to be taken into consideration prior to determining that at 5
years of age the cognitive deficit was due to one exposure and at 7 years of age it was due to a
different chemical . . . . Thus, Panel members cautioned about identifying any one specific
chemical as the main one associated with the cognitive deficits observed at 7 years of age in the
Columbia cohort.” 2012 SAP Minutes at 42.

- “[T]hese three epidemiologic studies 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.” 2012 SAP Minutes at 50.
4.2.3. Limitations and Uncertainties Raised in 2012 Federal Peer Review

The 2012 Federal Peer Review, established to review one of the Columbia Study analyses (Rauh et al. 2012) on research done that involved brain MRIs of a subset of the Columbia Study cohort, also noted several limitations and other concerns, including the following:

- “The results [of Rauh et al (2012)] must be interpreted very cautiously since there were only 6 males in the high exposure group and 9 in the low exposure group . . . . The study only used a general IQ measure to quantify cognition in this study and more specific cognitive and behavioral tests would be needed to pinpoint specific cognitive processes affected by CPF exposure.” Comments from Dr. Freund to EPA Aug. 3, 2013 Request for Peer Review at 1-2.
- The homogeneity of the sample in [Rauh et al (2012)] “may not be appropriate for generalizing to a larger urban population . . . . The sample is not ‘low risk’ based on the association between maternal poverty (or SES/environment) and child neural development. This further impacts the generalizability of the findings, and need for future research with larger samples and other populations.” Comments from Dr. Bitsko to EPA Aug. 15, 2012 Request for Peer Review at 1.
- “The high chlorpyrifos group had average prenatal lead exposure of 1.4 µg/dl compared to 0.8 µg/dl in the low exposure group. While these levels are not considered elevated, there is evidence that even low levels of lead can impact neurodevelopment, and even that the observed neurobehavioral deficits are more pronounced at lower blood lead levels when compared with higher blood lead levels . . . It is reported that lead was not associated with chlorpyrifos; however, given the sample size, this may not be a reliable finding.” Comments from Dr. Bitsko at 1–2 (citations omitted) (emphasis added).
- “The Rauh et al, 2006 paper provided . . . no information . . . regarding the qualifications of the individuals who administered and scored the [psychological] tests. The Rauh et al. 2011 paper did not provide any information regarding the administration, scoring, or qualifications of the individuals who administered the IQ test . . . [E]xaminers [should] be familiar with the Standards for Educational and Psychological Testing and . . . complete graduate training in assessment or be supervised by such a person . . . . [E]xaminers [should] have specialized training when testing persons from unique linguistic, cultural, or clinical backgrounds.” Comments from Dr. Chelonis to EPA July 23, 2012 Request for Peer Review at 1.
- “[G]iven that the sample of children used in the Rauh et al. studies had very different characteristics than that of the samples on which these [psychological] measures were standardized, caution should be used when describing the results, especially when attempting to
generalize these findings to the general population.” Comments from Dr. Chelonis at 2.

- “[N]o information was reported regarding the means or standard deviations of the samples, hence it is not possible to compare these data to the population norms . . . . The main uncertainties around the outcome measures stem from the fact that those measured were standardized on a sample that was very different than the sample that was used in the Rauh et al. research . . . . Unfortunately, the Rauh et al. 2011 study did not report any means or standard deviations for overall IQ or for any of the subtests . . . . The main issue here is that outliers can greatly influence the slope of the function.” Comments from Dr. Chelonis at 3–4.

4.2.4. EPA Recognized that Significant Uncertainties and Limitations Made Use of the Epidemiology Studies Questionable for Risk Assessment Purposes.

In January 2013, subsequent to the PHHRA, 2008 SAP, 2012 SAP and 2012 Federal Peer Review, EPA summarized many of its concerns regarding the quality of the epidemiology studies, particularly the Columbia Study.

Thus far, EPA has not encountered epidemiological data of sufficient quality to support quantitative risk assessment of conventional pesticide chemicals. Before EPA decides how to use the epidemiological data on chlorpyrifos, we believe it is critical to attempt to resolve questions about these studies regarding the extent of cohort members’ exposures to chlorpyrifos, as well as the impact of exposure to other compounds capable of causing or contributing to the observed neurological outcomes. . . . The July 2012 SAP report is in accord with EPA’s assessment that the Agency should attempt to resolve certain key questions about the epidemiological data. Specifically, the SAP recommended that EPA pursue a number of possible approaches for attempting to resolve whether the neurological outcomes observed in the studies occurred in the absence of AChE inhibition – the effect EPA’s current regulatory approach is designed to preclude. Further, given that the women and children studied in the Columbia University-sponsored epidemiology study were exposed to multiple chemicals (including other pesticides, polycyclic aromatic hydrocarbons and lead), the SAP cautioned the agency about attributing the outcomes to a single chemical based on the current analysis conducted by Columbia University researchers. These statements by the SAP lead the agency to believe that we need to further explore the extent to which the observed neurological outcomes were influenced by exposure to these other chemicals.

Bradbury letter at 3–4. See also EPA’s January 2013 Status Report, In re Pesticide Action Network N. Am., et al. v. U.S. EPA, No. 12-71125 (“EPA’s 2013 Status Report”) at 2-3 (9th Cir. Jan. 29, 2013), ECF No. 18-1. (“[I]t is critical for EPA to attempt to resolve questions about the cohort members’ exposure to chlorpyrifos and other compounds, including other organophosphate pesticides and unrelated toxins,
before determining to what extent it can use the epidemiological studies in its ongoing full weight of the evidence analysis for its Human Health Risk Assessment . . . .” (emphasis added)).

4.3. EPA Repeatedly Sought the Raw Data for the Columbia Study to Determine Whether the Study Could Be Used for Risk Assessment Purposes.

EPA repeatedly stated, including to the United States Court of Appeals for the Ninth Circuit, that the Agency needed to secure the raw data3 from the Columbia Study in order to determine whether the study could be used for the Agency’s human health risk assessment; however, those efforts were repeatedly rejected by the Columbia researchers:

- “Following receipt of the [2012 SAP] report EPA began conducting a number of analyses to address [its] recommendations . . . . [The Agency is] making progress in conducting a dose-reconstruction analysis of potential exposures to the women and children studied in the Columbia University-sponsored epidemiology study in order to assess the degree to which the individuals in the cohort may or may not have been exposed to chlorpyrifos levels high enough to cause AChE inhibition. In addition to this assessment, to address the SAP recommendations EPA also intends . . . to complete an evaluation of cohort exposures to other chemicals. In 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 that information 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.” Bradbury letter at 4 (emphasis added).

- “EPA explained that it will need to analyze the raw data from the Columbia University study as part of its human health risk assessment for chlorpyrifos. To date, the study authors have declined to provide the data, but . . . EPA is hopeful that the data will be provided.” EPA’s 2013 Status Report at 3 (emphasis added).

- “EPA has made progress on the dose reconstruction analysis. However, the analysis of the biomarker of exposure data and evaluation of the multi-chemical exposures suggested by the [SAP] necessitate that EPA obtain the raw data from the [Columbia] epidemiology study. At this time, EPA only has access to summary information provided by the publications, but has been working to obtain the original data from the study authors to conduct the needed analysis.”
The raw data from the Columbia Study were particularly critical to EPA’s efforts because this was the first time that the Agency had attempted to use epidemiology in a quantitative risk assessment for a pesticide. See Housenger Decl. ¶ 8 ("[T]he Agency has generally not included epidemiologic data from literature studies in its quantitative risk assessment process for pesticides because these data have traditionally not been sufficiently robust and reliable for quantitative dose response assessment due to inherent uncertainties and limitations in such information. . . . [T]he issues raised . . . with respect to quantitative use of epidemiologic data are truly novel for the regulation of pesticides in the United States.").

4.4. April 15, 2013 Meeting Between EPA and Columbia Researchers Produced None of the Raw Data that EPA Had Sought.

In its Revised Human Health Risk Assessment for Chlorpyrifos dated December 29, 2014 ("RHHRA"), EPA disclosed for the first time that twenty months earlier the Agency had met with the Columbia researchers during an “all-day” meeting in New York City. RHHRA App. 6. For the most part, the circumstances of this meeting are a mystery. EPA did not provide public notice of the meeting. Neither Dow AgroSciences nor, to Dow AgroSciences’ knowledge, any other registrant of chlorpyrifos was advised of the meeting or invited to attend. Upon information and belief, none of the members of the 2008 SAP, 2012 SAP or 2012 Federal Peer Review were invited to attend the meeting. Id. There are apparently no minutes or transcripts of the meeting. There are no entries in EPA’s administrative docket for chlorpyrifos that reference or otherwise evidence the meeting. Moreover, there were apparently “additional discussions with [Columbia] staff” after the meeting, see RHHRA App. 6, p. 391, but no references to those discussions appear in the administrative record.4

EPA’s closed-door meeting with Columbia researchers did not result in the production of the raw data EPA repeatedly said it needed to be able to use the Columbia Study in the Agency’s human health risk assessment. To the contrary, EPA learned several details from the Columbia researchers that create even more significant uncertainty as to the Columbia Study.

3 Specifically, “EPA requested the original analytic data file used to support analyses presented in the peer-reviewed, published epidemiology studies concerning in utero chlorpyrifos exposure (V. Rauh et al., 2011; V.A. Rauh et al., 2006; Whyatt et al., 2004).” See EPA’s RHHRA App. 6, p. 384.

4 Under these circumstances, it is surprising that EPA claims that it “performed its review and critical evaluation of [the] epidemiology studies in an open and transparent manner.” RHHRA at 33.
First, EPA learned that the Columbia researchers had no data relevant to the “agency’s need to determine whether the levels of chlorpyrifos exposure in the environment . . . [of the] study participants were above or below levels that may elicit a greater than 10% inhibition of acetylcholinesterase enzyme levels, the current regulatory endpoint.” RHHRA App. 6, p. 386. The Columbia researchers estimated pesticide exposure, but not in a way meaningful to EPA’s data needs. RHHRA App. 6, p. 386.

Second, EPA learned that data regarding pesticide product use among cohort participants was of “such poor quality” that it was of no use in assisting EPA “to better understand the pattern and frequency of organophosphate pesticide use among cohort participants.” RHHRA App. 6, p. 387.

Third, EPA “learned from unpublished, supplemental analyses performed by [Columbia] researchers upon EPA request that postnatal blood lead levels and prenatal chlorpyrifos levels are also not strongly statistically associated (Andrews, January 21, 2013)” RHHRA App. 6, p. 388 (emphasis added). However, those data are not included in the RHHRA and it does not appear that EPA has them. There is thus no way for registrants or the public to test the data or EPA’s reliance on them.

Fourth, EPA learned that the Columbia researchers had no data regarding the impact of postnatal exposures to polycyclic aromatic hydrocarbon (“PAH”) on neurodevelopmental outcomes. Thus, the meeting did not fully address the 2012 SAP’s “concern that [the Columbia] authors had not fully considered the long-term effects of [PAH] exposure . . . .” RHHRA App. 6, p. 389. The Columbia researchers apparently expressed their “belief” to EPA that prenatal, not postnatal, exposure to PAH is more relevant to neurodevelopmental outcomes, but provided no data for the Agency to verify that “belief.” RHHRA App. 6, p. 389.

4.5. Notwithstanding the Lack of Raw Data, EPA Relied on the Epidemiology Studies to Increase the PHRRA FQPA Safety Factor from 1X to 10X.

In its RHHRA, EPA concluded that “chlorpyrifos likely played a role in the neurodevelopmental outcomes reported by the epidemiologic study (Columbia University) investigators.” RHHRA at 6. Numerous limitations and uncertainties, several of which have been discussed herein, “preclude definitive causal inference,” according to the Agency. See, e.g., RHHRA at 6, 49. However, “there is sufficient uncertainty in the human dose-response relationship for neurodevelopmental effects which prevents the Agency from reducing or removing the statutory 10X FQPA Safety Factor. The FQPA 10X Safety Factor will be retained for infants, children, youths, and women of childbearing age for all exposure scenarios.” RHHRA at 49.5
It is clear that the epidemiology studies, particularly the Columbia Study, played a critical role in EPA’s decision to retain the 10x FQPA safety factor. See, e.g., RHHRA at 49 (“Given the totality of the evidence, the agency concludes that chlorpyrifos likely played a role in the neurodevelopmental outcomes reported by the Columbia University investigators. . . .”). However, as discussed herein, the epidemiology studies have numerous uncertainties and limitations, including EPA’s inability to review the studies’ underlying data in order to validate the reported results, making the Agency’s reliance on the studies to set a safety factor both scientifically and legally inappropriate.

5 EPA said as part of its FQPA safety factor decision that there is “sufficient uncertainty in the human dose-response relationship for neurodevelopmental effects to prevent the Agency from reducing or removing the statutory 10X FQPA safety factor.” RHHRA at 6-7. However, in light of the Agency’s PHHRA’s determination that there were sufficient, reliable data to support a 1X Safety Factor, the more appropriate analysis is whether the Agency has met its burden of showing that it has sufficient, reliable data to increase the Safety Factor from 1X to 10X. § 408(b)(2)(C)(ii), 21 U.S.C. § 346a(b)(2)(C)(ii).

EPA’s reliance on the epidemiology studies, particularly the Columbia Study, to increase the preliminary FQPA safety factor from 1X to 10X for chlorpyrifos is rife with procedural and scientific deficiencies. As set forth in detail below, these deficiencies include:

- EPA relied on an epidemiology study that has numerous and significant deficiencies for risk assessment reliance purposes.
- EPA failed to obtain raw data from the Columbia researchers that the Agency repeatedly stated it needed to appropriately assess the Columbia Study’s role, if any, in the risk assessment for chlorpyrifos. The Agency compounded this error by conducting a closed-door undocumented meeting with the Columbia researchers, learning at that meeting of additional significant limitations and uncertainties with the Columbia Study, and still relying on it for FQPA safety factor purposes. This lack of transparency is particularly troubling because it could serve as potential precedent for future registration actions, undermining public confidence in the registration process and discouraging the development of new pesticide products.
- EPA’s FQPA safety factor determination contravenes EPA and other government policies with respect to data access and transparency in scientific decision-making.
- EPA failed to provide a reasonable, science-based explanation for abandoning its determination in the PHHRA that a robust, complete data set supported an FQPA safety factor of 1X.
- EPA failed to follow through on numerous recommendations for follow-up study that would have allowed it to either clarify many of the uncertainties in the Columbia Study, or allow the Agency to totally discount it in the risk assessment process.
- EPA’s RHHRA does not address a number of important studies submitted by DAS, raising further concerns as to whether its decision-making was based on complete and reliable scientific data.

5.1. The Columbia Study is Replete with Deficiencies that Limits its Scientific Validity, and EPA’s Failure to Address these Deficiencies is Contrary to Agency Policy.

EPA’s reliance on the Columbia Study to form the basis for its safety factor conclusions in the RHHRA is problematic because the Columbia Study has a number of significant deficiencies that diminish its scientific validity. Notably, the Columbia Study failed to account for socioeconomic and other factors unique to the Study’s cohort, factors that undermine the generalizability of the Study’s
results to the broader U.S. population. That the RHHRA did not even mention this issue is particularly glaring in view of the fact that a federal peer reviewer questioned whether the study’s conclusions were generalizable to a larger urban population, much less the broader U.S. population. See Comments from Dr. Bitsko to EPA Aug. 15, 2012 Request for Peer Review at 1. As discussed in greater detail in Section 8, below, as well as in comments submitted by Gradient (to docket EPA-HQ-OPP-0850, April 2015), incorporated by reference here, additional limitations and uncertainties include, but are not limited to:

- The Study’s failure to consider alternative explanations for observed neurodevelopmental outcomes, including exposure to other chemicals and other key risk factors, see infra Section 8.2.2;
- The Study cannot be replicated because it is based on outdated exposure circumstances that no longer exist and have not existed in the U.S. for nearly 15 years, see infra Section 8.7;
- The analytic method used to measure chlorpyrifos exposure in blood has not been validated at the low concentrations reported, see infra Section 8.2.1;
- The Study’s small sample size generates instability in risk estimates and limited an analysis of potential confounding factors, including lead, see Gradient Comments on RHHRA (J. Goodman, H. Lynch, and L. Rhomberg) (“Gradient Comments”);
- EPA failed to address inconsistencies across the epidemiological studies and a lack of coherence with the toxicological data, which do not support a causal link between chlorpyrifos exposure and neurodevelopmental effects below those associated with AChE inhibition, see Gradient Comments;
- EPA’s evaluation of the epidemiological studies does not establish a biologically plausible mode of action (“MOA”), see Gradient Comments; see also infra Section 6.2;

In addition to raising concerns about whether the RHHRA’s conclusions are rooted in sound science, EPA’s failure to appropriately consider or address a number of these issues is contrary to Agency policy. Specifically, EPA’s own guidance for incorporating epidemiology in human health risk assessments instructs that particular attention be paid to, inter alia, the quality of the exposure assessment, generalizability of study results, and the effect of modifying factors. See Transmittal of Meeting Minutes of the FIFRA Scientific Advisory Panel Meeting on the Draft Framework and Case Studies on Atrazine, Human Incidents, and the Agricultural Health Study: Incorporation of Epidemiology and Human Incident Data into Human Health Risk Assessment at 8 (Apr. 22, 2010) (“[P]articular attention must be paid to the quality of epidemiologic studies. Relevant considerations include, but are not limited to: . . . the quality of the exposure assessment, including validation measures if available; . . . adequate
consideration of and control for . . . the effect modifying factors; and . . . the potential for the study to be
generalized to other populations.”); see also EPA Draft Framework for Incorporating Epidemiologic &
Incident Data in Human Health Risk Assessment at 15–20 (Jan. 7. 2010) (recommending that an
evaluation of human studies for risk assessment consider key factors, including, inter alia, exposure
assessment methods, confounding factors, and external validity/generalizability).

5.2. **EPA’s Failure to Obtain and Review the Raw Data for the Columbia Study Significantly
Undermines the Scientific Integrity of the Agency’s Weight-of-the-Evidence Analysis.**

EPA determined based on its meeting with the Columbia researchers that the Agency had “gained
additional information to better clarify and characterize the major issue areas identified as uncertainties.”
RHHRA, App. 6 at 391. Accordingly, “EPA decided that it would not further pursue its request for the
analytic data file from the [Columbia] researchers.” *Id.* Regardless how EPA has characterized its
decision, the fact of the matter is that the Agency’s 10X FQPA safety factor determination is based on
data that EPA has not seen and the chlorpyrifos registrants have not seen.⁶ By not looking at the raw data,
EPA will never know, for example, to what extent and which members of the Columbia cohort were
allegedly exposed to chlorpyrifos only after chlorpyrifos was phased out of residential use, to what extent
members of the cohort self-reported exposures to other OPs and lead. In addition, access to the
underlying raw data would allow for assessments of, among other things, potential biases, the magnitude
of potential confounders, whether the results of regression are sensitive to variations in the method used
to impute missing data, and whether the Columbia Study findings are sensitive to cut-points applied to
categorize exposure, outcome, and covariate variables. See *Measurement Errors and Misclassification in
Epidemiology Studies of Chlorpyrifos and Neurodevelopmental Outcomes*, at 8–10 (J. Goodman & C.
Loftus). EPA will never know how this information would affect its ability to rely on the study. In other
words, EPA’s decision to forego obtaining and reviewing the raw data casts a huge cloud of doubt over
the scientific integrity of the Agency’s risk assessment process in this matter.

Strict regulations requiring EPA access to raw data govern the Agency’s review of studies
submitted by registrants to obtain or maintain pesticide registrations. *See 40 C.F.R. § 169.2 (k).* EPA
would never base a significant registration decision on a registrant study for which it had no ability to
review the underlying data. Yet with respect to chlorpyrifos, the Agency is subjecting the third-party
Columbia Study to a different standard of regulatory review in making registration decisions. EPA
regulatory action based on studies for which there is no access to the underlying data is simply unfair by

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⁶ Requests by DAS to EPA and the National Institutes of Health for the raw data from the Columbia
Study, excluding any personal information, were denied.
any measure, especially where, as here, the study suffers from numerous uncertainties and other limitations. The Agency’s position is particularly troubling in light of the fact that the Columbia Study was carried out with Federal funds.

The fact that the Columbia Study (and additional epidemiology) appears as a journal article does not change the fact that EPA must review the underlying (raw) data. Most credible experts agree that simply because studies are “peer reviewed” and published does not ensure that they are based on sound science; if the underlying raw data are unavailable and cannot be confirmed to be valid and reproducible, any published articles based on those data cannot be assumed to be based on sound science. Indeed, in other contexts, EPA has stated that published literature, without the raw data, is insufficient to judge the validity of the study. See Pesticide Programs; Pesticide Registration and Classification Procedures; Application Procedures to Ensure Protection of Data Submitters’ Rights, 49 Fed. Reg. 30,884, 30,896 (Aug. 1, 1984) (“Published research typically describes the test methods and presents the results of the research in summary form. Such articles, however, rarely offer the detailed information (such as raw data results) needed by the Agency to reach sound conclusions about the risks and benefits of the pesticide, and to judge the validity of the study. . . . When long-term studies are involved, journal articles alone will rarely suffice for registration purposes.”). A parade of challenges to registrations on the basis of studies for which there is no available underlying scientific support could follow an EPA registration action regarding chlorpyrifos that does have the benefit of an analysis of the underlying data.

That the Columbia researchers engaged in oral discussions with EPA about the Study does not change the result that EPA does not have the raw data to test the conclusions in the study. Just as EPA would not rely solely on the impressions and beliefs of a registrant about the meaning of the studies it had submitted without access to the raw data, EPA should not do so here. As well-intentioned as the Columbia researchers may be, their biases and beliefs simply cannot be tested by the Agency without access to the raw data that it had repeatedly requested. “To be reasonable, scientific judgment may not be based on mere speculation but must take into account relevant information and data.” EPA Determination of the Appropriate FQPA Safety Factor(s) in Tolerance Assessment at A-8 (Feb. 28, 2002).

EPA’s failure to gain access to the underlying raw data is particularly problematic here because the Columbia Study is epidemiology. The Agency’s use of epidemiology in risk assessment is new, untested, and potentially precedent-setting. Indeed, the Agency has characterized its use with respect to chlorpyrifos as a matter “on the frontiers of science.” Vogel Decl. at ¶ 5. (emphasis added). See also Housenger Decl. ¶ 8 (“[T]he quantitative use of epidemiologic data [is] truly novel for the regulation of pesticides in the United States.”); Transmittal of Meeting Minutes of the FIFRA Scientific Advisory Panel...
Meeting on the Draft Framework and Case Studies on Atrazine, Human Incidents, and the Agricultural Health Study: Incorporation of Epidemiology and Human Incident Data into Human Health Risk Assessment at 34 (Apr. 22, 2010) ("OPP has not yet completed a [weight-of-the-evidence] approach that also includes epidemiology or human incident data like that proposed in . . . the draft framework.").

Moreover, epidemiology does not prove causation and has other inherent limitations. See, e.g., In re Actos (Pioglitazone) Prods. Liab. Litig., No. 12-cv-00064, 2014 WL 60324, at *11 (W.D. La. Jan. 7, 2014) ([E]pidemiological studies . . . do not, and cannot, present conclusions as to causation.); see also EPA DRAFT Framework for Incorporating Human Epidemiologic & Incident Data in Health Risk Assessment (Jan. 7, 2010) ("EPA Framework") at 20 ("[M]ost epidemiology studies suffer some limitations in size, scope, exposure assessment, or data analysis which prevent their use in quantitative risk assessment.") (citation omitted); Housenger Decl. ¶ 8 ("[T]he Agency has generally not included epidemiologic data from literature studies in its quantitative risk assessment process for pesticides because these data have traditionally not been sufficiently robust and reliable for quantitative dose response assessment due to the inherent uncertainties and limitations in such information.").

Even when epidemiology is so limited it cannot be used quantitatively, its qualitative use is still subject to scientific integrity and transparency and must represent the “best available data.” See EPA Framework at 6, 27 ("OPP intends to employ . . . epidemiology studies . . . in its human health risk assessment. Consistent with [the] Administrator[‘s] . . . commitment to transparency and scientific integrity, OPP’s goal is to use such information in the most scientifically robust and transparent way. . . . [I]n the [weight-of-the-evidence] analysis, OPP will use the best available data across multiple lines of evidence . . . ”) (emphasis added).

Because of the inherent limitations of epidemiology, its use in risk assessment analysis must be met with great caution and scrutiny. This is especially true when EPA determines that it needs the raw data, but those data are not provided to the Agency. Indeed, EPA has addressed for a weight-of-the evidence analysis the relative weight that should be accorded to studies for which underlying data are not available: “[w]hen animal and epidemiologic data do not provide a consistent toxicological picture of a particular pesticide, more weight would likely be given to those studies with robust study design and availability of replication or confirmatory data.” EPA Framework at 31. Under this approach, an epidemiology study, like the Columbia Study, that has many uncertainties, has not been replicated, and for which there are no underlying, confirmatory data falls far short in the weight-of-the-evidence approach when compared to a complete, scientifically robust data set, for which the underlying data are available, like the one that the Agency relied upon in its PHHRA to set the FQPA safety factor at 1X.
Moreover, EPA’s Framework makes it clear that no one study should overwhelm the Agency’s weight-of-the-evidence analysis: “OPP plans to use a [weight-of-the-evidence] analysis for evaluating epidemiology and human incident data, such that all available data are evaluated and conclusions are made on the preponderance of the information rather than relying on any one study.” EPA Framework at 27. EPA has failed to meet that standard when it relies on one study—the Columbia Study—to alter the conclusion it had reached as to the FQPA safety factor in the PHHRA on the basis of a complete, scientifically robust data set. That failure is particularly egregious when the Agency cannot even look at the underlying data for the one study that it relies upon to alter a prior conclusion that was based on a complete, scientifically robust data set.7

Finally, as noted earlier, FQPA safety factor determinations pursuant to Section 408(b)(2) of the FFDCA—including those determinations that have the effect of revoking a tolerance—must be based on “valid,” “complete” and “reliable” data. “Reliable” data are data that “must be sufficiently sound such that OPP could routinely rely on such information in taking regulatory action.” EPA Determination of the Appropriate FQPA Safety Factor(s) in Tolerance Assessment at A-6 (Feb. 28, 2002). Without the raw data underlying the Columbia Study, EPA cannot determine that the study is valid, complete or reliable, and therefore whether it scientifically supports its determination of a FQPA safety factor of 10X in the RHHRA. Indeed, by not looking at the Columbia Study’s raw data, the Agency has, in essence, created the uncertainty upon which it bases the FQPA 10X Safety Factor.

To the knowledge of Dow AgroSciences, EPA has never before increased a preliminary FQPA safety factor determination from 1X to 10X for a pesticide based on epidemiology, and certainly not epidemiology for which the Agency has no ability to review and validate the raw data. Such precedent-setting action should be subject to close scrutiny. The Supreme Court has made it clear that agencies have an obligation in fulfilling their statutory mandates to “examine the relevant data and articulate a satisfactory explanation for [their] action[s] including a rational connection between the facts found and the choice made.” Motor Vehicle Mfrs. Ass’n of U.S., Inc. v. State Farm Mut. Auto. Ins. Co., 463 U.S. 29, 43 (1983) (citations and internal quotations omitted) (emphasis added). Under the Administrative Procedure Act, “an agency rule would be arbitrary and capricious if the agency has relied on factors which Congress has not intended it to consider, entirely failed to consider an important aspect of the

7 Included in the RHHRA is a March 8, 2010, memorandum from the Columbia Center for Children’s Health to EPA noting that the federal government had granted $568,000 to pool and analyze the raw data from the Columbia Study, Mt. Sinai Study and CHAMACOS Study. See RHHRA at 265. This memorandum notes that the principal investigator for this study is one of the authors for the CHAMACOS Study. RHHRA at 265. Now, five years later, the results of this new study have never been published. Even more troubling is that the raw data from the Columbia Study have been provided to another researcher for analysis, at great taxpayer expense, but are still not available to the EPA for use in making very significant regulatory determinations.
problem, offered an explanation for its decision that runs counter to the evidence before the agency, or is so implausible that it could not be ascribed to a difference in view or the product of agency expertise.” *Id.* See also *Love v. Thomas*, 858 F.2d 1347, 1358–59 (9th Cir. 1988) (reversing an EPA order suspending a pesticide registration based in part on agency’s reliance on insufficient data).


Reliance upon the Columbia Study in the absence of a full review of supporting data not only vitiates EPA’s statutory mandates under the FQPA, FIFRA and FFDCA, but it sets a precedent totally contrary to previous EPA regulatory policy. In particular, EPA’s own guidance for assessing the quality of scientific information received from non-agency sources directs the Agency to evaluate, among other factors, whether the “complete data set [is] accessible.” *See A Summary of General Assessment Factors for Evaluating the Quality of Scientific and Technical Information*, EPA 100/B-03-001, at 7 (June 2003), available at: http://www2.epa.gov/sites/production/files/2015-01/documents/assess2.pdf

These Assessment Factors were designed to complement the EPA’s *Guidelines for Ensuring and Maximizing the Quality, Objectivity, Utility, and Integrity of Information Disseminated by the Environmental Protection Agency*, EPA/260R-02-008 (Oct. 2002), developed pursuant to the Data Quality Act (“DQA”), Section 515 of the Treasury and General Government Appropriations Act of 2001, Pub. L. No. 106-554 (codified at 44 U.S.C. § 3516 note). The DQA was enacted to improve the quality of information disseminated by federal agencies. Specifically, the Act requires federal agencies to “issue guidelines ensuring and maximizing the quality, objectivity, utility, and integrity of information (including statistical information) disseminated by the agency” and to “establish administrative mechanisms allowing affected persons to seek and obtain correction of information maintained and disseminated by the agency that does not comply with the guidelines.” *Id.* Accordingly, in fulfilling its regulatory mandate to protect human health, EPA must also ensure that it satisfies its statutory obligations under the DQA.

Following passage of FQPA, then Vice President Al Gore, on behalf of the President, directed EPA to work together with the U.S. Department of Agriculture “to ensure that implementation of the paramount public health goals of the new law is informed by a sound regulatory approach” among other factors and, to that end, identified specific implementation principles, such as the following:

- basing regulatory decisions on “the best science and data that are available;”
- ensuring that the use of default assumptions and exposure scenarios are “carefully considered and fully explained in the public record;”
- recognizing “the discretion provided in the current law” when evaluating whether or not to remove or reduce the presumptive tenfold safety factor, exercising that discretion “in a manner consistent with the intent of Congress and the 1993 [NRC] Report,” and utilizing external scientific review panels “[i]n developing analytical approaches for the exercise of that discretion;”
- “clearly and fully” communicating approaches “in a manner that facilitates informed review by all affected constituencies;” and
- ensuring that, “[w]here there must be a selection among competing or alternative approaches or interpretations in implementing the law, alternatives should be fully presented and explained before moving forward.”

Food Quality Protection, Mem. for Secretary Daniel R. Glickman and Administrator Carol M. Browner from the Vice President, April 8, 1998.

Perhaps recognizing that an evaluation of the data underlying the Columbia Study was critical to EPA’s risk assessment, Agency officials requested the analytic data file used to support the study’s conclusions regarding the health effects of chlorpyrifos exposure. However, the Columbia researchers refused to provide the data. Instead, the Columbia researchers and EPA officials held a closed-door meeting in which they discussed the Agency’s questions about the data to determine whether further review was necessary. See RHHRA App. 6 to 384. As a result of information gathered during this meeting, EPA stated that it was “no longer pursuing the request for the original analytic data file from CCCEH researchers.” Id. Beyond this cursory explanation, EPA provided no information detailing the substance of the discussions that took place at the meeting, and no meeting minutes or transcripts from the meeting were made publicly available.

EPA’s uncharacteristic approach to transparency, in addition to being contrary to its own regulatory policy, is also diametrically opposed to the Administration’s policy on scientific integrity. In his March 2009 Memorandum on Scientific Integrity, President Obama stated:

> If scientific and technological information is developed and used by the Federal Government, it should ordinarily be made available to the public. To the extent permitted by law, there should be transparency in the preparation, identification, and use of scientific and technological information in policymaking.

EPA Administrator Jackson echoed the EPA’s commitment to upholding the values of scientific integrity in a follow-up memorandum to EPA employees, in which she stated:

I believe that the methodologies and guidelines that EPA uses for scientific analyses should be shared fully with the public. Our regulatory decisions should include a full explanation of the science issues addressed by the Agency, the data relevant to those issues, and the interpretations and judgments underlying the Agency’s scientific findings and conclusions.

Mem. to EPA Employees, Scientific Integrity: Our Compass for Environmental Protection, Lisa P. Jackson (May 9, 2009).

The Administration’s policy on scientific integrity was reinforced in a February 2013 Memorandum from Dr. John P. Holdren, Director of the White House Office of Scientific and Technology Policy, in which Dr. Holdren expressed the Administration’s recognition that federally funded research and scientific data should be made available to the public. See John. P. Holdren, Mem. for the Heads of Exec. Dep’ts and Agencies, Increasing Access to the Results of Federally Funded Scientific Research (Feb. 22, 2013). Dr. Holdren’s Memorandum directed federal agencies to develop a plan for increasing access to scientific data and detailed objectives for agencies to incorporate into their respective data access plans. These objectives included ensuring that “all extramural researchers receiving Federal grants and contracts for scientific research and intramural researchers develop data management plans, as appropriate, describing how they will provide for long-term preservation of, and access to, scientific data in digital formats resulting from federally funded research” and “[i]nclud[ing] mechanisms to ensure that intramural and extramural researchers comply with data management plans and policies.” Id. at 5 (emphasis added).

Finally, Dow AgroSciences is concerned that EPA’s use of epidemiological studies for which the Agency lacks supporting data and that are refuted by an abundance of quantitative science sets a double standard for academic researchers and members of the regulated community. EPA commonly requests raw data from pesticide registrants on studies they submit, and Dow AgroSciences and other registrants routinely provide and maintain such data for Agency review to ensure a thorough, high-quality risk assessment. Not holding federally-funded researchers to the same standard creates a glaring inconsistency in light of EPA’s stated principles of scientific integrity in regulatory matters and raises serious due process concerns with respect to the Agency’s revised risk assessment for chlorpyrifos in the absence of the underlying epidemiology data. See Indus. Safety Equip. Ass’n v. EPA, 656 F. Supp. 852, 865 (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.”).

5.4. EPA Failed to Provide a Reasonable, Science-Based Explanation for Changing its Preliminary Human Health Risk Assessment Safety Factor Determination of 1X.

EPA’s 2011 PHHRA found an FQPA safety factor of 1X to be appropriate because, inter alia, the “toxicological database for chlorpyrifos is extensive and is adequate to support the registration review,” there were “no residual uncertainties in the exposure database,” and the database showed that the “dietary risk assessment is conservative and is not expected to underestimate dietary exposure to chlorpyrifos and chlorpyrifos oxon.” PHHRA at 36, 40. Yet EPA’s RHHRA, issued three years later, provides absolutely no explanation as to how this reliable and complete data set is no longer supportive of a 1X Safety Factor. Indeed, the RHHRA does not even mention the 1X discussion in the PHHRA. Instead, EPA relied on the Columbia Study, with its plethora of limitations and uncertainties, to the apparent exclusion of the prior complete toxicology data set, not to mention several new studies submitted by the registrant and discussed in Section 5.7 below. EPA’s use of one epidemiology study to negate a reliable robust set of traditional toxicology data is also inconsistent with EPA’s framework for the consideration of epidemiology in risk assessment.8

EPA’s 10X Safety Factor determination in its RHHRA is not only contrary to reliable and transparent scientific methodology, but it is also inconsistent with EPA’s past policy and practice with respect to the setting of the safety factor for pesticides. From 1996 to 2012 EPA “made pesticide tolerance decisions for 412 pesticides and, in 308 or 75 percent of the cases, [EPA] applied . . . a 1-fold or 3-fold safety factor . . . .” U.S. Gov’t Accountability Office, GAO - Committee on Environment and Public Works, 13-254, Environment Health: EPA Has Made Substantial Progress but Could Improve Processes for Considering Children’s Health (“GAO Report”) at 37 (2013). The 1X Safety Factor was applied in 61 percent (251) of those pesticide tolerance decisions. GAO Report at 38. These statistics are consistent with prior Agency statements regarding its desire to use reliable data to make careful case-by-

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8 Notably, while the meeting minutes of the 2012 FIFRA SAP include an apparent Panel recommendation that the FQPA safety factor be increased to 10X, the transcript reveals that such a recommendation was not discussed. In fact, when the issue of the FQPA safety factor was raised by a panel member, it was quickly determined that the panel should focus on scientific uncertainties associated with the Columbia Study, and not related policy issues like the FQPA safety factor. See Transcript of the 2012 FIFRA Scientific Advisory Panel Open Meeting on Reevaluation of the Scientific Issues Associated with Chlorpyrifos Health Effect, at 615, 618–19 (April 10–12, 2012).
case analyses of the appropriate safety factor, rather than simply make the 10X safety factor a default determination:

Where reliable data are available, . . . OPP has the discretion to choose between the default approach and an individualized assessment. OPP, as a policy matter, prefers not to simply apply a default value in making decisions under section 408 where reliable data are available that support an individualized determination . . . For these reasons, where reliable data are available, OPP favors an approach that attempts to make a specific case-by-case determination as to the size of the additional factor rather than rely on the 10X default value . . . OPP believes that careful analysis of the completeness and quality of the existing databases should, in most instances, account for uncertainties including FQPA considerations such that OPP will not have to rely on the additional 10X value as a default.

EPA DRAFT Determination of the Appropriate FQPA Safety Factor(s) for Use in the Tolerance-Setting Process at 16 (May 1999). See also EPA Safety Factor Guidance at A-4, n. 7 (“Contrary to statements in the NAS Report . . . , an additional 10X factor has not been automatically applied by OPP or EPA whenever a study identified fetal developmental effects.”).

And when EPA has applied greater than a 1X safety factor, it has been for reasons not applicable to chlorpyrifos. In fiscal year 2011, for example:

all the FQPA safety factor decisions to retain all or part of the safety factor were made based on one of the following three rationales: (1) the use of a “lowest observed adverse effect level (LOAEL)” instead of a “no observed adverse effect level” . . . (2) a data gap, meaning one or more required toxicity study was not complete, . . . (3) studies [that] did not test the required duration of exposure, and extrapolation was required.

GAO Report at 65. “[B]ased on the weight-of-evidence, often a value of 3X is used to address database deficiencies for pesticides, given the large amount of data typically available.” EPA Safety Factor Guidance at 9–10 (emphasis added) (citation omitted).

In response to questions raised by Congress with respect to implementation of the FQPA safety factor during passage of the statute, EPA made it clear that:

When the data are incomplete, we use an additional uncertainty factor between three and ten based on how much information is incomplete. The data EPA would consider include data submitted in compliance with EPA testing requirements, available data published in the scientific literature, and any other data available to EPA and meeting general scientific standards.

9 In light of the abundant uncertainties that are attendant to the Columbia Study, and the fact that this is the first time EPA has ever used epidemiology to set an FQPA safety factor, EPA also should have explained why a 10X Safety Factor is more appropriate than a 3X Safety Factor.
Ironically, in the case of chlorpyrifos, as set forth in detail herein, EPA is without sufficient data from Columbia to determine whether the Columbia Study “meet[s] general scientific standards.” What EPA does have are reliable data submitted with respect to the very endpoints of concern—data which EPA has said would be dispositive in assessing any potential pre and postnatal toxicity to infants and children:

Where reproductive and developmental data have been found acceptable by EPA, and the data do not indicate potential pre or postnatal effects of concern, the additional tenfold margin of safety would not be applied.

_Id._ Where “reliable data” establish that a lower margin of safety will meet the FQPA safety standard, and EPA elects to apply the extra tenfold factor, the burden shifts to EPA to justify its decision. This is precisely the showing that the Agency has failed to make with respect to chlorpyrifos.

Based on this history, EPA’s safety factor determination for chlorpyrifos marks a major policy shift. When determinations based on such a policy shift are founded on scientifically flawed data to which the Agency has no access, both the policy shift and its resulting determinations become inherently suspect.

5.5. **EPA Failed to Follow Through on Numerous Recommendations that Would Have Added Scientific Clarity to the Columbia Study.**

The 2008 SAP, 2012 SAP and 2012 Federal Peer Review made several recommendations to EPA in order to help address uncertainties and limitations in the epidemiology studies. It does not appear that any of these recommendations were followed. These recommendations included:

- In order to eliminate the possible causes of neurodevelopmental effects by other pesticides in the Columbia Study, it is suggested that EPA should repeat the pre-post residential cancellation analysis done for chlorpyrifos using other pesticide measurements, such as malathion diacid . . . , a specific metabolite of malathion. The outcomes from those additional analyses will either confirm or reject EPA’s preliminary conclusion that chlorpyrifos is likely to play a role in the neurodevelopmental outcomes. 2012 SAP Minutes at 48.
- The Panel “urged the Agency to find ways to use the epidemiology studies, and in particular, the data from the Columbia Study, to inform the dose-response assessment of chlorpyrifos.” 2012 SAP Minutes at 50.
- “The Panel suggested additional research that could answer the critical question of whether chlorpyrifos induces neurodevelopmental effects in humans at doses that do not cause AChE inhibition . . . . This study could be easily performed by EPA researchers, or by others.” 2012 SAP Minutes at 53.
- “[I]f there are data available on other environmental exposures (other pesticides, etc.), the association between these exposures and the outcomes should be studied.” Comments from Dr. Bitsko to EPA Aug. 15, 2012 Request for Peer Review at 2.
- “In general, it is agreed that the research requires replication (as stated by authors and in the EPA review).” Comments from Dr. Bitsko at 2.
- “A between group analysis using inferential statistics . . . should be performed . . . . This would be the most direct and least problematic method for determining whether exposure to chlorpyrifos resulted in significant decreases in IQ or significant increases in behavioral problems. If significant differences were found between the groups, this would provide much stronger evidence than the evidence that is currently provided by the analyses that were presented in the Rauh, et al. 2006 and the Rauh, et al. 2011 papers. Comments from Dr. Chelonis to EPA July 23, 2012 Request for Peer Review at 5.

When the Agency does not follow through on expert recommendations, such as these, its decision-making becomes suspect.


With respect to the EPA’s application of the FQPA safety factor to its occupational risk assessment for chlorpyrifos, DAS reiterates the scientific, legal, and policy concerns detailed above with respect to basing a safety factor determination on epidemiology studies for which: (i) the Agency lacks the underlying raw data; (ii) numerous limitations and uncertainties exist that undermine the reliability of the studies for use in a registration action; and (iii) EPA has failed to follow numerous recommendations designed to determine whether the studies are suitable for use in a risk assessment. Epidemiology which is unreliable for these reasons for use in resetting the FQPA safety factor at 10X is similarly not reliable
Reliability of data is also critical for EPA’s risk-benefit assessment under FIFRA. In addition to its obligation under FFDCA to ensure that tolerance decisions are informed by “reliable data,” EPA has an obligation under FIFRA to ensure that any public review to develop a risk-benefit evaluation of a pesticide or any of its uses must be “based on a validated test or other significant evidence raising prudent concerns of unreasonable adverse risk to man or the environment,” an obligation that exists “[n]otwithstanding any other provision of [FIFRA]”. FIFRA § 3(c)(8), 7 U.S.C. § 136a(c)(8) (emphasis added). Studies which EPA is unable to confirm and replicate through access to and review of raw data fall far short of this standard of a “validated test or other significant evidence.”

5.7. EPA Failed to Consider Several Critical Studies in its Revised Human Health Risk Assessment.

In its RHHRA, EPA did not address or even mention several critical studies submitted to EPA, raising further concerns as to whether EPA has satisfied its obligation to ensure that its risk assessment is based on complete and reliable scientific data.

In particular EPA’s RHHRA makes no reference to two critical drinking water studies (discussed in greater detail in Section 12, below) submitted to EPA. The first study was a toxicological study that demonstrated no risk from exposure to chlorpyrifos-oxon in drinking water. In this study, no hazard was found at doses 7-times the level of chlorpyrifos that could actually be found in drinking water based on the water solubility of chlorpyrifos. Consistent with EPA’s determination of no risk from potential volatilization, no hazard thus equates to no risk from potential exposures through drinking water. In the second study, based on 47,000 water samples from available water monitoring surveys of community water systems on both large to small rivers and streams taken during various time periods between 1991 and 2013, statistical methods allowed the characterization of the distribution of exposures at the higher percentiles of exposure. Exposures dropped to only slightly above 10% of both the acute and chronic levels of concerns. The results matched well with exposures based on CDC biomonitoring data. The results of this study thus raise serious questions about the soundness of EPA’s assumption that [the automatic?] reliance on drinking water modeling results that come within an order of magnitude of monitoring results is not an overly conservative practice.

10 “EPA intends to apply risk assessment techniques developed in implementing the Food Quality Protection Act of 1996 . . . to any pesticide risk assessment, whether it falls under FQPA or not, so long as application of the risk assessment technique is consistent with good scientific practice and is not otherwise prohibited by law.” EPA Pesticides: Health and Safety, Worker Risk Assessment at 1 (April 2014).
These studies were submitted in June and August of 2014, respectively, but the RHHRA’s drinking water assessment failed to consider or even mention either study. EPA’s failure to consider the oxon study was particularly baffling in view of the fact that EPA provided comments on the study design and participated in a discussion of the study’s results.

It is also concerning that several comprehensive reviews on chlorpyrifos (Eaton et al. 2008; Li et al. 2012; Prueitt et al. 2012) and which yield perspective on neurodevelopmental effects in experimental studies, exposure, and weight of evidence frameworks were not cited in the recent RHHRA, and, apparently, not considered by the Agency. A thorough Agency review should have incorporated such reviews, and these need to be seriously considered in further revisions of the risk assessment for chlorpyrifos.

Under the Administrative Procedure Act, agency actions will be deemed arbitrary and capricious where they “entirely fail[ ] to consider an important aspect of the problem.” Motor Vehicle Mfrs. Ass’n of U.S., Inc. v. State Farm Mut. Auto. Ins. Co., 463 U.S. 29, 43 (1983). This includes an agency’s failure to consider available studies or data that are relevant to the issue under consideration. Id.

EPA’s failure to evaluate these important studies, generated at great expense to the registrant, is also contrary to its own policy. Just four months ago, EPA said with respect to another chlorpyrifos-related study that:

[i]t is important to recognize that when EPA receives significant data that represent a clear advancement in risk-assessment methodology, . . . EPA cannot simply ignore such submissions in the name of meeting a previously estimated timetable. Even if EPA were inclined to make such a decision, it is unlikely EPA could defend any decision that failed to consider a significant development that was presented to it before completing its response.11

Consistent with this Agency statement—made to a U.S. Court of Appeals—EPA’s disregard of these critical studies in preparing its RHHRA for chlorpyrifos is indefensible.12

EPA’s failure to consider these reliable and well-reasoned scientific studies is particularly astounding when viewed in light of EPA’s reliance on unreliable and incomplete epidemiological data to increase the FQPA safety factor. DAS urges EPA to carefully review these studies and reconsider the conclusions in its RHHRA, particularly those concerning risks from drinking water exposures. At the very least, if for some unknown reason, EPA elects not to address these studies, the Agency must be

11 Vogel Decl. at ¶ 13.

12 Conversely, how can EPA reasonably rely on the Columbia Study, which the Agency can neither replicate nor validate, to make risk assessment decisions that involve “novel scientific questions” on the “frontiers of science”? Vogel Decl. at ¶ 13.
prepared to explain that decision and how its conclusions concerning its exposure assessment for chlorpyrifos are supported by the complete universe of relevant scientific data available to the Agency.
6. EXPERIMENTAL TOXICOLOGY DOES NOT SUPPORT EPA’S USE OF A 10X SAFETY FACTOR.

Summary

- DAS commends the Agency’s incorporation and use of scientifically-derived and defensible data-derived extrapolation factors (“DDEFs”), or uncertainty factors, in the risk assessment for chlorpyrifos.

- A vast majority of the experimental studies that are cited as forming the basis for a proposed linkage between chlorpyrifos and effects on neurodevelopment have methodological/design challenges which severely limit their utility in a weight-of-evidence assessment. These factors include dose, inappropriate route of exposure and utility of a neurotoxic vehicle, factors which have been highlighted by Scientific Advisory Panels (SAP’s) as limiting the utility of reported results when considering relevance to humans.

- Most of the experimental studies (both in vitro and in vivo) cited as forming the basis for the alleged association between chlorpyrifos exposure and effects on neurodevelopment in children use dose levels that are tens of thousands of times higher than actual human exposures and hence there is little relevance of these studies when considering risk to humans.

- Several SAP reviews in addition to the RHHRA are consistent in their finding that a chlorpyrifos mode-of-action/adverse outcome pathway (MOA/AOP) leading to neurobehavioral effects cannot be established. This has led to the EPA stating that “uncertainties such as the lack of an established MOA/AOP for neurodevelopmental effects and the potential exposure to multiple-AChE-inhibiting pesticides preclude definitive causal inference.”

- Numerous independent reviews (including SAP reviews) have evaluated the body of data and purported studies/evidence that associate chlorpyrifos exposure with neurodevelopmental effects and there is consistency in the conclusion across these that protection against cholinesterase inhibition is protective of all other toxicities, including neurodevelopmental effects. Therefore, as the EPA notes in the RHHRA, acetyl-cholinesterase (AChE) inhibition remains the most robust quantitative dose response effect and thus continues to be the appropriate endpoint for use in quantitative risk assessment.

- There is strong evidence from the animal literature that AChE inhibition (RBC or brain from adult or offspring) is a sensitive endpoint that is protective of neurobehavioral, neuropharmacologic, and morphologic alterations. Importantly, regulatory standards for chlorpyrifos are established to limit human exposure to levels well below those causing AChE inhibition.

- The results of several studies have shown that the maximum concentration of chlorpyrifos oxon residues that could be present in drinking water has no potential for inhibition of tissue cholinesterase activity following ingestion of drinking water.

- There is not compelling scientific (animal or human) evidence or a proposed, tested, and validated mode of action to support either the contention that chlorpyrifos is associated with neurodevelopmental effects in humans or that there is a sound basis for retention of the 10X FQPA SF.
6.1. Toxicological Basis for Weight of Evidence Assessment Does Not Support Link with Neurodevelopmental Effects.

DAS commends the Agency for its consideration and adoption of specific advancements in science which has permitted the development and robust use of PBPK modeling, combined with estimates of human exposure, to yield DDEFs for chlorpyrifos. The continued and long-standing use of red blood cell cholinesterase inhibition (in this case 10%) as the sentinel and conservative \textit{(i.e.}, not associated with biological adversity or toxicity) point of departure may be appropriate for subsequent use in risk assessment, although DAS recommends that use of the actual biological target (brain ChEI) is more relevant to humans and should be considered as it has been (and implemented in decision-making) for other organophosphorous compounds. Together, the PBPK-PD model and accompanying estimates of 10% RBC ChEI in humans permit refined aPAD and cPAD values which are protective of human health.

However, in contrast to the application of advancements in science to derive refined permissible exposure levels to humans, EPA’s consideration of experimental toxicology studies in conjunction with reported epidemiological findings does not serve as a suitable and unifying basis for a weight of evidence determination that chlorpyrifos may be associated with claims of neurodevelopmental effects in humans. In addition, the components (USEPA, 2014) cited as forming the basis for retention of the 10X FQPA are not aligned to collectively support a position of associating chlorpyrifos exposure with neurodevelopmental effects. These key components include (a) experimental animal studies which have been reviewed by several EPA SAPs and for which no MOA or AOP can be defined or described and (b) epidemiological studies which are inconsistent in reported findings and which for one (Rauh et al 2006), the raw data and study details have never been publically presented or made available for independent review. The lack of scientific rigor, inclusion of speculation as the basis for reported epidemiological outcomes, and overall tenuous linkage of experimental data to infer an association between chlorpyrifos exposure and suggested adverse outcomes is potentially precedent-setting and fails to achieve a scientific standard upon which robust and transparent regulatory decision-making should be based.


It is important to critically assess studies published in recent years with respect to test design, dose, route of exposure, vehicle, and reported effects to determine whether there is both biological plausibility and coherence of findings relative to putative neurodevelopmental effects occurring through non-cholinergic mechanisms. For example, investigators of the Columbia University epidemiology study cite experimental work in animal models that associates chlorpyrifos exposure with effects on neurocognitive development in rats. (Rauh et al. 2006).
Experimental work showed links between chlorpyrifos exposure during pregnancy and deficits in fetal growth and neurocognitive development in rats.\textsuperscript{10} Prenatal chlorpyrifos exposure was shown experimentally to inhibit acetylcholinesterase, to downregulate muscarinic receptors, to inhibit the adenylate cyclase signaling cascade, to decrease brain DNA and RNA synthesis, and to suppress neurite outgrowth.\textsuperscript{10–14} Many organophosphate compounds are lipophilic and cross the placenta.\textsuperscript{15} Prenatal exposure is a source of concern because acetylcholinesterase seems to act as a neurotropic factor during brain development.\textsuperscript{16} Organophosphates may also disrupt brain development through noncholinergic mechanisms, at doses that cause only minimal acetylcholinesterase inhibition.\textsuperscript{16–18}

This statement serves as the biological basis for the alleged association between chlorpyrifos exposure and resultant effects on neurodevelopment in inner-city children from the Columbia cohort (\textit{Rauh et al.} 2006). It is important to review several of the above-cited studies to determine whether there is consistency in reported effects and how relevant the route of exposure and dosing regimens are for human exposure scenarios. Information that informs the utility of these studies when considering relevance to humans is contained in the following table:
### Section 6 Table 1. Studies cited by Rauh et al. (2006) as confirming neurodevelopmental effects in humans

<table>
<thead>
<tr>
<th>Citation</th>
<th>Route of Exposure</th>
<th>Vehicle</th>
<th>Dose</th>
<th>Dose-response evaluated</th>
<th>Cholinesterase Inhibition Measured</th>
<th>Effect(s) reported</th>
</tr>
</thead>
<tbody>
<tr>
<td>11: Dam et al., 1998</td>
<td>Subcutaneous (S/C)</td>
<td>DMSO 1 mL/kg</td>
<td>1 mg/kg</td>
<td>No</td>
<td>No</td>
<td>Reductions in DNA synthesis in brainstem, forebrain</td>
</tr>
<tr>
<td>12: Johnson et al., 1998</td>
<td>S/C</td>
<td>DMSO 1 mL/kg</td>
<td>1 mg/kg; 5 mg/kg</td>
<td>No</td>
<td>No</td>
<td>Alterations in RNA concentration/content in brainstem/forebrain</td>
</tr>
<tr>
<td>13: Slotkin and Seidler, 2005</td>
<td>S/C</td>
<td>DMSO 1 mg/kg</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Elevations in synaptic protein related to 5 HT at 5 months of age</td>
</tr>
<tr>
<td>14: Song et al., 1997</td>
<td>S/C</td>
<td>DMSO 1 mg/kg</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Deficits in multiple components of the adenylyl cyclase cascade</td>
</tr>
<tr>
<td>17: Huff et al., 1994</td>
<td>Cell culture</td>
<td>Acetone Up to 1 mM</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Interactions/binding to muscarinic receptors of rat striatum</td>
</tr>
<tr>
<td>18: Song et al., 1998</td>
<td>Cell culture</td>
<td>DMSO 1.4-140 uM</td>
<td>Yes</td>
<td>No</td>
<td>Inhibition of DNA synthesis</td>
<td></td>
</tr>
</tbody>
</table>

Several characteristics of these studies have importance when assessing their utility for extrapolation to humans and when assessing the comparison of these findings to whole animal guideline studies.

#### 6.3. Experimental Challenges – Route of Administration, Vehicle Not Relevant to Humans

It is well-acknowledged that many of the laboratory animal studies that have reported findings associated with neurodevelopment, including behavioral and cognitive effects, utilize a route of exposure
(subcutaneous) that is not of relevance to humans and which may result in more rapid and different delivery of chlorpyrifos to the systemic circulation, which ultimately reflects an artificial situation compared to the human scenario. In addition, there has been robust and consistent caution by both investigators and the USEPA Scientific Advisory Panel (2008; 2012) on the use of DMSO as a vehicle for delivery in *in vivo* studies.

For example, the OECD 2006 DNT 426 guideline specifically states: “The vehicle should not cause effects that could interfere with the interpretation of the study, neither be neurobehaviorally toxic…” However numerous animal studies that are used as the basis for reported neurodevelopmental concerns in humans use a vehicle, subcutaneous DMSO, that possesses neurotoxic properties at the doses used (1 mL/kg). The kinetic and neurobehavioral properties of DMSO present a significant confounding variable when neurotoxicity and neurodevelopment are the key endpoints of evaluation/investigation. Cavaletti et al (2000) have shown that ip administration of dilute solutions of DMSO can have a significant impact on the nervous system. They note that “The 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.” Other authors have shown that DMSO used as a dose vehicle can also enhance the clinical symptoms of organophosphates (*Ballough et al*. 2008; *Carr et al.* 2008).

Finally, in the 2012 EPA SAP, the Panel stated that “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.”

### 6.4. Experimental Dose and Lack of Relevance to Humans

In the 2010 EPA Draft Framework for Incorporating Human Epidemiologic and Incident Data in Health Risk Assessment (USEPA, 2010), the Agency specifically states that “Risk is a function of both the hazard of a chemical and the levels of exposure to a chemical.” This is of relevance given that the RHHRA for chlorpyrifos is just that—an assessment of risk to humans from exposure to chlorpyrifos. It is important to review those *in vitro* and *in vivo* toxicological studies that have been conducted and which purportedly demonstrate findings related to neurodevelopment, in conjunction with estimates of human exposure, to understand the magnitude of difference which exists between experimental exposures and actual human exposure levels.
The common dose of chlorpyrifos used in many of these in vivo studies (1 mg/kg) is more than 16,000 times higher than the actual 95th percentile exposure (0.06 ug/kg bw/day) to children (Barr et al. 2005).

Eaton et al. (2008) notes that “for purposes of assessing current risks to chlorpyrifos, daily exposure rates in the general population, excluding farmers and their children, are expected to be less than 0.01 ug/kg/day.” Putting this into perspective with the NOAEL of 1 mg/kg/day for neurodevelopmental effects in experimental animal studies (EPA, 2012; Li et al. 2008) yields a margin of exposure (MOE) of 100,000.

Only a few of the studies cited by Rauh et al. (2006) employed a range of doses, so that even within the limitations of these experimental systems and designs, there is little or no potential for assessing dose-response.

Critical to the question of whether non-cholinergic effects may be operating at dose levels below those at which detectable cholinesterase inhibition (ChEI) occurs, in only a few of the studies cited by Rauh et al. (2006) was ChEI concurrently measured. When measured, substantial inhibition of ChE was found to exist. In order to probe whether non-cholinergic mode(s) of action are operating independently of cholinergic mechanisms, there needs to be concurrent assessment of cholinergic activity.

The concentrations employed in the in vitro studies cited by Rauh et al. (2006) are much higher than biologically relevant concentrations and commonly were conducted without physiologically-relevant levels of albumin (chlorpyrifos binds to plasma proteins and albumin has chlorpyrifos-oxonase activity). For example, in vitro incubations of 1 µM chlorpyrifos are 100,000 times higher than the mean, circulating blood levels reported from residential use of this pesticide (3.9 pg/mL; Whyatt et al. 2005).

While the EPA presents in vitro and in vivo study evidence in the RHHRA that supports their proposed position that chlorpyrifos likely played a role in the neurodevelopmental outcomes in the Columbia Study, they recognize the challenge with dose levels used in these experimental studies. As stated in the RHHRA at 158:

In summary, in the late 2000s, a number of papers were published on the in vitro modification of various proteins by chlorpyrifos or chlorpyrifos oxon. Although interesting and provocative, these studies were usually conducted with exceedingly high concentrations (high micromolar to millimolar) of the OP compound, making the connection to a ‘real world’ human exposure tenuous.
As an aside to this discussion, DAS would note that in the RHHRA, there appears to be an error in the following statement, which is relevant when comparing exposure levels associated with neurodevelopmental outcomes and cholinesterase inhibition. As stated, “It is notable, however, that comparing the lowest NOAEL observed in the \textit{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 and AChE inhibition suggests that AChE inhibition is a sensitive endpoint.” While we agree that cholinesterase remains the most sensitive endpoint for point of departure and risk assessment, the Billauer-Haimovitch et al study (2009) does not include a dose level of 0.2 mg/kg/day; rather the lowest administered dose was 1 mg/kg/day and again the dosing regimen used DMSO as vehicle and subcutaneous administration, both which have profound challenges relative to evaluation of neurodevelopmental toxicity and relevance to humans.

In summary of this previous discussion, DAS contends that the body of experimental toxicological data cited by Rauh et al. (2006) and UESPA is confounded by design challenges and exposure relevance to humans, both of which preclude forming a sound scientific basis for the subsequent association between chlorpyrifos exposure and neurodevelopmental outcomes in humans.

6.5. \textbf{External Reviews of Experimental Toxicology Studies Do Not Support Link Between Neurodevelopmental Effects and Chlorpyrifos Exposure.}

Over the last 10+ 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. From a broad perspective, it is difficult to comprehend how non-cholinergic mode(s) of action could be operating and exerting adversity at levels below the threshold for inhibition of cholinesterase and why such putative effects, manifesting themselves on a whole animal level, have not 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 40 years as part of the registration and reregistration process for chlorpyrifos.

A preponderance of the experimental animal work that has been published over the past 15 years has come from the laboratory of Dr. Slotkin and associates and, while this work has produced a variety of reported effects resulting from chlorpyrifos exposure (typically at levels 1 mg/kg or above), there has not been a consistent hypothesis-driven research aim that has sought to probe non-cholinergic effects and whether such effects occur below the threshold for cholinesterase inhibition. The variety of potential targets and reported findings are numerous, wide-ranging and include muscarinic/nicotinic receptors, serotonin receptor dynamics, signaling intermediates such as G proteins and adenylate cyclase, protein
kinases, components of cell energetics and nuclear transcript factors, among others (reviewed in Slotkin 2004 and Slotkin et al. 2006). The presumption of non-cholinergic effects occurring at sub-threshold levels for cholinesterase inhibition assumes the existence of various neurotoxicological targets that have greater affinity for chlorpyrifos than acetylcholinesterase at low systemic exposures. However, there are no known amino acid or protein targets that have been identified that would be consistent with such a proposed multi-site molecular mechanism. Chlorpyrifos has acetylcholine-like features and is a highly specific substrate for acetylcholinesterase. Research has demonstrated that acetylcholinesterase is the most sensitive target among serine hydrolases, neurotransmitter receptors, and other putative neurochemical sites.

The SAP (2008) recognized some of the challenges that accompany these investigative studies, particularly for how they might or might not assist with human health risk assessment. They noted that the following. 2008 SAP Minutes at 12.

Some members questioned the experimental methods used in some of the animal studies as well as the interpretation and application of the results of neurobehavioral testing in animals for risk assessment. It was acknowledged that the study outcomes could be affected by 1) the route of administration of chlorpyrifos, 2) the developmental period of exposure, 3) the methods used to measure changes in behavioral domains, and 4) the choice of dependent variables. Panel members agreed with the Agency’s expressed caution on the use of dimethyl sulfoxide (DMSO) as a vehicle because of its intrinsic toxicity and potential influence on absorption. In addition, uncertainty was expressed about potential interactions between DMSO and low doses of chlorpyrifos and the effect of this interaction on the developing animal.

Given the challenges relative to interpretation of many of the studies that have been published in recent years suggesting non-cholinergic effects from exposure, it is helpful to review the findings of the 2008 SAP and the Eaton et al. (2008) reviews relative to conclusions on neurodevelopment related to chlorpyrifos exposure.

The SAP concluded that gestational or early postnatal exposures can lead to neurochemical or behavioral alterations that persist into adulthood, although they noted that the studies reporting such effects must be considered in the context of exposure, experimental design, and other influencing variables, the very point DAS has presented earlier in these comments. Specifically, the SAP recommended that inhibition of cholinesterase be used as a point of departure until a mode of action is identified and validated for other putative endpoints or toxicological targets. Related to this, the SAP noted that the majority of these studies have been conducted at or above 1 mg/kg, a sufficient exposure for the inhibition of cholinesterase. The SAP recommended general collaborative efforts to determine if enzyme inhibition is occurring at discrete brain sites at critical periods of development in animals.
In addition to the SAP reviews, several independent reviews of the experimental toxicological literature (Eaton et al. 2008; Li et al. 2012) are available which demonstrate that there is more inconsistency than consistency in reported findings and importantly, that there is profound influence impacting reported effects owing to a range of exposure periods, dosing scenarios, testing strategies and specific methodologies and equipment used.

In their review, Li et al. (2012) concluded that “there is strong evidence from the animal literature that AChE inhibition (RBC or brain from adult or offspring) is a sensitive endpoint that is protective of neurobehavioral, neuropathologic, and morphologic alterations that were measured following gestational, lactational, and/or early postnatal exposure to 1 to 6 mg/kg-d.”

In reviewing much of the same literature, Eaton et al. (2008) concluded that most of the in vivo animal studies that report neurodevelopmental and/or behavioral effects occurred in the presence of brain and/or plasma cholinesterase inhibition, while the in vitro studies report effects at concentrations that exceed in vivo study exposures. Current global regulatory standards for chlorpyrifos are established to limit human exposure to levels well below those causing AChE inhibition. As such, many of the experimental in vivo studies have no immediate relevance to humans. Additionally, a few studies report effects on neuronal differentiation at levels below those associated with cholinesterase inhibition, but these still exceed human exposures. Eaton et al. (2008) summarized their review of this area stating that the weight of evidence from animal and in vitro studies suggest that neurodevelopment effects are secondary to cholinesterase inhibition.

A recent hypothesis-based weight-of-evidence evaluation (Prueitt et al. 2012) of the neurodevelopmental effects of chlorpyrifos has been published and concluded that a causal association between chlorpyrifos exposure and neurodevelopmental effects in the absence of cholinesterase inhibition in the brain is not plausible in humans, and that the few associations observed in epidemiology studies are most likely attributable to alternative explanations.

In summary of this discussion on putative non-cholinergic mechanisms from experimental studies, many of the studies that have reported 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.

6.6. Absence of a Defined Mode of Action/Adverse Outcome Pathway

DAS agrees with the 2008 SAP that the literature that has explored and reported on neurodevelopmental/neurobehavioral findings in vitro and in vivo, is not anchored or supported by an
identifiable, validated, and replicated biologically plausible mode of action at levels below AChE depression. This is also a critical point to the human relevance framework and whether results in animal studies can and should be extrapolated to humans. The 2008 SAP Panel concluded the following relative to this question (2008 SAP Minutes at 28):

There 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.

And then from the 2012 SAP (2012 SAP Minutes at 15.), the Panel stated that:

[T]he number of available neurobehavioral studies is limited leading to caution concerning this finding. Also, many of these studies are statistically under-powered and prone to Type I errors and should be discounted in formulating the weight of evidence for or against neurobehavioral effects from developmental exposure to chlorpyrifos. The Panel also expressed caution with the significance of some of the experimental neurotoxicological outcomes that have not been validated. These included tests of anxiety, depression, and social interactions. The Panel recommends these experimental outcomes be regarded as exploratory, and hypothesis-generating, as opposed to being evidence of toxicity. The lack of specificity in the direction of the neurobehavioral dose response findings is a problematic issue.

There appears to be continual inconsistency in how the animal toxicological literature is used in decision-making by EPA. While the limitations and experimental challenges of these studies have been widely acknowledged by independent review boards and EPA SAP Panels, there are persistent instances in which EPA cites selective studies in support of the position that the animal data points to potential neurodevelopmental effects resulting from chlorpyrifos exposure. For example, in the RHHRA, the Agency cites studies which possess the same experimental challenges that preclude the use of these studies for qualitative or quantitative weight of evidence decision-making. To illustrate, the Agency focuses on two studies (page 27 of the RHHRA) that provide some insight on the relative degree of cholinesterase inhibition, but one (Slotkin et al. 2013) again uses a dose of 1 mg/kg/day and uses the same challenging experimental regimen (subcutaneous with DMSO as vehicle). Another study (Ohishi et al. 2013) that is cited and noted by the Agency as using ‘relatively low doses’ of administered chlorpyrifos (0.36 mg/kg) notes a LOAEL of 0.36 mg/kg/day for RBC inhibition, but this is for dams and upon evaluation of the study, the NOAEL for offspring for the same endpoint (1.86 mg/kg/day) is much higher but not clearly cited by the Agency. Moreover, what is not brought forward are the authors’ specific notation that the dam NOAEL is about 2800 times higher than the estimated consumption of CPF through food in the general population and in pregnant women as examined in Japan. The salient point is the
importance of comparing experimental doses and NOAELs in experimental studies to actual human exposures which invariably yield large Margins of Exposure (MOEs). In closing, it is also concerning that several comprehensive reviews on chlorpyrifos (Eaton et al. 2008; Li et al., 2012; Prueitt et al. 2012) and which yield perspective on neurodevelopmental effects in experimental studies, exposure, and weight of evidence frameworks were not cited in the recent RHHRA. A thorough Agency review should have incorporated such reviews and that these need to be seriously considered in further revisions of the risk assessment for chlorpyrifos.

In the RHHRA (RHHRA at 27), the Agency states:

Overall, across the literature on neurodevelopmental outcomes and including the most recent publications, there continue to be inconsistencies in effects in relation to functional domains, dosing paradigms, and gender-specificity. The only studies reporting effects use doses that inhibit fetal/pup brain activity to some degree, even though there are also negative effects at the same doses. The broad profile of neurological effects that have been reported do not aid in the development of a specific AOP (AChE inhibition or other mechanisms), and existing experimental studies have not been designed to examine and track possible mechanisms from early initiating event to the final neurological outcome.

The Agency goes on to state that “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.” Id. at 31.

Finally, the Agency has stated in the RHHRA that “The SAP concurred with the Agency in 2008 and 2012 about the lack of definable key events in a MOA/AOP leading to neurobehavioral effects. The Agency has considered the new literature since the 2012 SAP related to mechanistic hypotheses as described below (Appendix 11), and note that such a MOA/AOP still cannot be established.” Id. at 27.

6.7. Recent Studies Show No Toxicological Effect of Chlorpyrifos-Oxon at the Highest Levels that Could Be Found in Drinking Water.

In the recent chlorpyrifos Oxon drinking water study (Marty et al. 2014), the potential for the oxon degradate of chlorpyrifos to elicit cholinesterase inhibition in RBC was investigated. The route of exposure utilized was drinking water, to match the oral intake pattern of this compound as a potential residue in treated drinking water.

Historically and across many regulatory agencies globally, risk assessments for chlorpyrifos are based on cholinesterase (ChE) inhibition in RBC. As shown in Figure 1, effects in RBC are somewhat conservative, but consistent with those of nervous system tissues, such as brain. Data from a recent comparative cholinesterase study (Marty et al. 2012) show substantially different profiles of ChE
inhibition for chlorpyrifos and Oxon, highlighting the chemical and toxicokinetic differences between these two chemicals.

At a common dose of 10 mg/kg (acute), chlorpyrifos causes 87% inhibition of RBC ChE and 48% inhibition of brain ChE (Marty et al. 2012) (Figure 1). In contrast, Oxon causes complete (> 99%) inhibition of RBC ChE and no measureable inhibition of brain ChE. This pattern shows 10x increased sensitivity of RBC to Oxon, but 3x lower sensitivity in brain.
Section 6 Figure 1. Comparison of ChE inhibition in RBC and brain tissue of adult female SD rats following a single bolus gavage dose of: Top) chlorpyrifos (CPF) or Bottom) chlorpyrifos oxon (Oxon). Note: all data is from Marty et al. (2012), except for 40 mg/kg Oxon brain data (*) from an earlier study (Costa et al. 1998)
It is likely that these differences in ChE inhibition profiles are due to the lack of systemic bioavailability of Oxon up to high dose levels of 10 mg/kg. In contrast, a small percentage of an oral dose of chlorpyrifos is known to become systemically bioavailable (Marty et al. 2012), (Mendrala et al. 1998).

A recent review by EPA describes the primary route of metabolism as dearylation to 3,5,6-trichloropyridinol (TCP) (US EPA: Health Effects Division, Office of Pesticide Programs, 2008). A minor route of metabolism, desulfurylation, produces the reactive metabolite chlorpyrifos oxon. A good example dataset showing the high degree of first-pass metabolism of chlorpyrifos is from the radiolabeled experiment of Mendrala and Brzak (Mendrala et al. 1998). These authors found TCP represents ~99% of the total of TCP, chlorpyrifos and chlorpyrifos oxon in blood of rats 3 h post-dosing after administration of 3 or 63 mg/kg chlorpyrifos via oral gavage in corn oil. Chlorpyrifos levels were approximately 1% of total and only trace levels of chlorpyrifos oxon (<0.1% of total) were found (Fig. 2). Oxon concentrations peaked at or before the T_max for chlorpyrifos in blood, indicating rapid hydrolysis of this metabolite in vivo (Mendrala et al. 1998).

**Section 6 Figure 2.** Relative percentages of TCP, chlorpyrifos (CPF) and chlorpyrifos oxon (OXON) in the blood of adult Male F344 rats 3 h after administration of CPF via oral gavage.

In contrast, no detectable Oxon is found in blood samples taken from rats administered Oxon at the time of peak ChE inhibition (Marty et al., 2012). This poor bioavailability is probably due to an extremely high first-pass, chemical and/or enzymatic loss of Oxon. Sites of loss could be within the GI tract.
contents, enzymatic metabolism by enterocytes, in the splanchnic capillary blood supply and/or during first-pass transit through the liver (Fig. 3).

Section 6 Figure 3. Sites of Presystemic Hydrolysis of Oxon

Sites of Presystemic Hydrolysis of Chlorpyrifos Oxon:
1) aqueous phase of GI contents
2) enzymes in GI
3) carboxylesterases in Gut tissue
4) PON-1 esterase in Gut tissue
5) Enzymes/proteins in portal blood
6) Liver CYPs and esterases

Systemic circulation - No detectable Oxon (Marty 2012)
Overall, the lack of ChE inhibition in the brain, coupled with the lack of systemically available test material, shows that Oxon undergoes high first-pass metabolism at bolus gavage dose levels ≤ 0.5 mg/kg. This finding is consistent with results from (Atterberry et al. 1997) who reported age-related increases in liver carboxylesterase and P450 activity, which contribute to protection of target acetylcholinesterase and metabolism/inactivation of Oxon, respectively.

As stated above, the potential effects of Oxon residues in drinking water were then examined in a subsequent animal study. Marty and Bartels (2014) (followed by Marty and Marshall (2014)) exposed rats to up to 7 times the maximum possible concentration of Oxon in drinking water (based on chlorpyrifos water solubility). Over the 12 h sampling period (0, 1, 2, 4, 8 and 12 h post-dosing), there was no significant inhibition of RBC ChE at any time point with a 1.0 mg/L CPFO drinking water exposure (Figure 4). Based on these data, a time-of-peak ChE inhibition could not be determined. This study found no toxicological effect, therefore, no hazard at the highest levels that could conceivably be found in drinking water.

Section 6 Figure 4. RBC ChE Activity Following CPFO Drinking Water Exposure

Based upon previous toxicokinetic data (Marty et al., 2012), there is evidence that CPFO is not systemically bioavailable via the oral route, except at very high doses, due to rapid and complete first-
pass hydrolysis. This was seen in the previous comparative cholinesterase study (Marty et al., 2012) where there were no biological effects in systemic tissue (i.e., brain) after a 10 mg/kg dose of CPFO (gavage). The results of the recent Oxon drinking water study, which did not detect RBC ChE inhibition following exposure to 1.0 mg/L CPFO in drinking water, indicate that Oxon levels were not sufficiently bioavailable to affect ChE activity in RBC.

RBC ChE activity has been shown to be representative and conservative of numerous other systemic tissues with respect to CPFO-induced ChE inhibition (Table 2). In vitro data (Chambers et al., 2013; Chandra et al., 1997) indicate that multiple tissues exhibit similar sensitivity to CPFO-induced ChE inhibition. This supports the conclusion that the lack of RBC and/or brain ChE inhibition represents an absence of bioavailable CPFO at these tissues.

Section 6 Table 2. Inhibitory concentrations (IC50 values) of chlorpyrifos-oxon on cholinesterase activities in several rat tissues (Chambers et al. 2013).

<table>
<thead>
<tr>
<th>Tissue</th>
<th>IC50, nM</th>
<th>SD</th>
<th>95%CI</th>
<th>Tissue conc. mg or µl/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AChE</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brain</td>
<td>3.77</td>
<td>0.1</td>
<td>3.65-3.89</td>
<td>1</td>
</tr>
<tr>
<td>Duodenum-flushed</td>
<td>3.72</td>
<td>0.21</td>
<td>3.48-3.96</td>
<td>1</td>
</tr>
<tr>
<td>Duodenum-not flushed</td>
<td>4.17</td>
<td>0.48</td>
<td>3.63-4.71</td>
<td>1</td>
</tr>
<tr>
<td>Esophagus-flushed</td>
<td>3.13</td>
<td>0.31</td>
<td>2.78-3.48</td>
<td>1</td>
</tr>
<tr>
<td>Esophagus-not flushed</td>
<td>3.28</td>
<td>0.59</td>
<td>2.61-3.95</td>
<td>1</td>
</tr>
<tr>
<td>Stomach-flushed</td>
<td>4.08</td>
<td>0.09</td>
<td>3.98-4.19</td>
<td>1</td>
</tr>
<tr>
<td>Lung-perfused</td>
<td>7.21</td>
<td>1.32</td>
<td>5.72-8.70</td>
<td>2.5</td>
</tr>
<tr>
<td>Lung-not perfused</td>
<td>8.57</td>
<td>0.85</td>
<td>7.60-9.53</td>
<td>2.5</td>
</tr>
<tr>
<td>Heart-perfused</td>
<td>3.06</td>
<td>0.05</td>
<td>3.01-3.12</td>
<td>2.5</td>
</tr>
<tr>
<td>Heart-not perfused</td>
<td>3.91</td>
<td>0.05</td>
<td>3.85-3.97</td>
<td>2.5</td>
</tr>
<tr>
<td>Diaphragm</td>
<td>6.64</td>
<td>0.28</td>
<td>6.33-6.96</td>
<td>3.8</td>
</tr>
<tr>
<td>RBC</td>
<td>4.19</td>
<td>0.69</td>
<td>3.41-4.97</td>
<td>0.7</td>
</tr>
<tr>
<td>RBC ghosts</td>
<td>5.08</td>
<td>0.32</td>
<td>4.72-5.45</td>
<td>37.5</td>
</tr>
<tr>
<td>Plasma</td>
<td>55.36</td>
<td>0.51</td>
<td>54.78-55.94</td>
<td>12.5</td>
</tr>
<tr>
<td>Brain 1</td>
<td>3.07</td>
<td>0.28</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plasma 1</td>
<td>273.4</td>
<td>14.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liver (total ChE) 1</td>
<td>1930</td>
<td>250</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1 Data from Chandra et al., 1997
In summary, chlorpyrifos Oxon has been shown to have only presystemic exposure and effects in rats, following oral bolus administration at dose levels greater than 0.1 mg/kg. Subsequent evaluation of potential cholinesterase inhibition of Oxon residues present in drinking water were negative, with no RBC effects found upon a full time-course analysis in rats ingesting the maximum possible water concentrations of this test material via *ad lib* intake of drinking water. Since RBC is defined as the endpoint affording conservative estimate of chlorpyrifos or oxon effects (US EPA 2014 RHHRA), these study results show that Oxon residues have no potential for inhibition of tissue cholinesterase activity following ingestion of drinking water.

6.8. Summary

In summary, DAS proposes that the approach and basis for the Agency’s conclusion that chlorpyrifos likely played a role in the neurodevelopmental outcomes from the Columbia Study and which support use of the 10X FQPA safety factor are tenuous, confusing, and lack scientific support and rigor. The scientific rationale and explicit delineation of how animal studies with experimental design and exposure challenges, ones with no discernible or even speculative mode of action related to potential effects on neurodevelopment, are supportive of questionable findings in one epidemiology study is unclear and untenable. EPA even notes in the RHHRA that “uncertainties such as the lack of an established MOA/AOP for neurodevelopmental effects and the potential exposure to multiple-AChE-inhibiting pesticides preclude definitive causal inference.” RHHRA at 6.

DAS encourages the Agency to review the critical independent analyses (*Eaton et al.* 2008; *Li et al.* 2012; *Prueitt et al.*, 2012) that have assessed both epidemiological and animal studies related to neurodevelopmental outcomes and which have consistently concluded that, based on either current human exposures or those used in experimental studies, protection against cholinesterase inhibition is sufficiently protective against any putative neurobehavioral or neurodevelopmental effects. Whereas the Agency has preliminarily concluded that chlorpyrifos may have played a role in the effects observed in the epidemiology studies, we emphasize that the effects could more probably be due to random variability, other environmental exposures and problems associated with exposure assessment. Therefore, DAS respectfully disagrees with the preliminary Agency conclusion that “these lines of evidence together support a conclusion that exposure to chlorpyrifos results in adverse neurodevelopmental outcomes in humans, at least under some (still unclear) conditions.” RHHRA at 49.
Section 6 References


Carr, R. L. and Nail, C. A. 2008. Effect of different administration paradigms on cholinesterase inhibition following repeated chlorpyrifos exposure in late preweanling rats. Toxicol Sci 106, 186-92,


7. **EPA’S USE OF PBPK MODEL TO CALCULATE DATA-DERIVED EXTRAPOLATION (UNCERTAINTY) (UF) FACTORS (“DDEFs”) WAS APPROPRIATE, BUT SHOULD ALSO BE APPLIED TO PREGNANT WOMEN IN OCCUPATIONAL SETTINGS.**

**Summary:**

- DAS agrees with the Agency’s use of the well-validated PBPK/PD model for derivation of Data-Derived Extrapolation (DDEF), (commonly referred to as Uncertainty Factors (UF)) for chlorpyrifos.

- The Agency’s comments about inability to use this approach for derivation of DDEF values for pregnant workers has been addressed with updates to the PBPK/PD model.

- Evaluation of predicted RBC cholinesterase inhibition effects during the three trimesters of pregnancy indicate little to no increased sensitivity to biological effects of chlorpyrifos, relative to non-pregnant women.

- The existing intraspecies Uncertainty Factor (UF$_h$) value of 4x for male and female adults should therefore be protective of pregnant women in occupational settings.

- In utero exposure to chlorpyrifos has been shown to be up to 2-3 fold lower than maternal levels measured in a human epidemiology study, consistent with 2-3 fold lower systemic exposure and resulting cholinesterase effects seen in rat fetuses vs. dams.

7.1. **EPA Appropriately Used the PBPK-PD Model to Derive DDEFs.**

As stated above, we agree with the Agency’s acceptance and use of the Multi-Route PBPK/PD model to calculate Data-Derived Extrapolation Factors (“DDEFs”) for chlorpyrifos RBC cholinesterase effects in humans in the RHHRA:

In the case of chlorpyrifos and the oxon, the PBPK-PD model provides the opportunity to use a data-derived approach (USEPA, 2014). Specifically, the PBPK-PD model accounts for PK and PD characteristics to derive age, duration, and route-specific human equivalent doses or concentrations, depending on the route of exposure, which serve as the Points of Departure (PODs) for risk assessment purposes. Consistent with EPA’s cholinesterase policy, acetyl cholinesterase (AChE) inhibition at a level of 10% is considered an adverse effect which is used as the threshold of regulation. The PBPK-PD model was used to define what dose level results in 10% red blood cell (RBC) AChE inhibition following 21 sequential days of exposure for a variety of occupational and residential scenarios and lifestages. Once defined, margins of exposure (MOEs) were calculated using typical exposure assessment methods which use these scenario- and lifestage-specific PoDs and direct comparison to applicable exposures.

We agree that the model is appropriate for determination of 10% RBC cholinesterase inhibition POD across lifestages. We also agree with the Agency’s opinion that the model submitted for review in 2014
(Poet 2014) did not contain a description of gestational physiology needed to model the RBC POD in pregnant women at that time: (RHHRA at 7).

While the current PBPK-PD model accounts for age-related growth from infancy to adulthood by using polynomial equations to describe tissue volumes and blood flows as a function of age, the model does not include any descriptions on physiological, anatomical and biochemical changes associated with pregnancy. Due to the uncertainty in extrapolating the current model predictions among women of child bearing age, the Agency is applying the standard 10X intraspecies extrapolation factor for women of childbearing age. For all other relevant populations, the Agency has reliable data to reduce the standard 10x intra-species factor.

7.2. Dow AgroSciences Has Provided Data to Support Modification of the PBPK-PD Model to Include Gestational Lifestages.

To investigate the appropriateness of the default 10x DDEF, or Intraspecies Uncertainty Factor, for pregnant workers, the current Multi-Route PBPK/PD model was expanded to include systemic exposure and RBC effects predictions during all stages of human pregnancy. This Pregnancy PBPK model was then used to validate the applicability of the new 4x DDEF for the chlorpyrifos POD in human to pregnant women as well.

Changes were made in physiology in the PBPK model based on the relevance to CPF and CPF-oxon disposition and pharmacodynamics, and using well-established reference values for human pregnancy (Poet 2015). Model changes include:

- Addition of placenta and fetal compartments, which grow over the course of pregnancy.
- Pregnancy specific changes in the slow compartment, fat, and rapid compartments.
- Pregnancy specific changes in blood composition
  - Changes in blood composition result in increased blood volume, decreased hematocrit
  - Lipids, Triglycerides, and cholesterol increase – leads to changes in partitioning
- Pregnancy specific changes in metabolism
  - CYP450 enzyme levels in liver
  - PON1 activity levels in liver and plasma

These important changes are included in the CPF model for pregnancy, built on the lifestage platform so either age-specific parameters or initial body weight-specific parameters can be used as the initial condition at the beginning of gestation. All model additions, changes, mathematical implementations, and model code are included in the Pregnancy PBPK model report, submitted to the Agency in April, 2015 (Poet 2015). For all simulations in that report, either age was set to 30 years, or a body weight of 69 kg, consistent with US.EPA, 2015 and the Exposure Factors Handbook mean body weight for females (US EPA 2011, Table 8-5).
7.3. **Comparison of RBC Cholinesterase Inhibition Dose-Response Across Gestational Lifestages.**

The Pregnancy model was then used to evaluate the appropriateness of DDEF values in a two-step process. First, an initial assessment was conducted to evaluate the exposure required to result in a 10% inhibition of RBC cholinesterase activity in average non-pregnant and pregnant females (1st, 2nd and 3rd trimesters), from all three routes of exposure (oral, dermal and inhalation). Second, a more comprehensive analysis was conducted by examining the variation in the RBC POD for a simulated pregnant woman cohort (n=10,000) by the oral and dermal exposure routes. The oral route was chosen based in the results of the average female model analysis and to compare to the non-pregnant DDEF evaluation conducted by DAS (Price 2014) and by the Agency (US EPA 2014). The dermal route analysis was also conducted, as this is a significant exposure route for occupational scenarios.

The results of the average female analysis are shown in Figure 1 below. Overall, the output from the Pregnancy PBPK model for non-pregnant women matches the output presented by the Agency in the Revised Human Health Risk Assessment (US EPA 2014). From oral exposures, some slight increased sensitivity in the RBC POD is seen, only in the 3rd trimester of pregnancy, with the dose required for 10% RBC cholinesterase inhibition approximately 10% lower than for non-pregnant women, or those in their 1st or 2nd trimester. Following dermal exposures, only women in their 2nd trimester are shown to have an RBC POD lower than non-pregnant women (<10% difference). Inhalation exposures to chlorpyrifos result in comparable RBC response in all non-pregnant and pregnant cohorts evaluated.
Section 7 Figure 1. Dose-response of peak RBC cholinesterase inhibition in non-pregnant women and women during the three trimesters of pregnancy, via oral, inhalation and dermal routes of exposure (data from Poet 2015).
7.4. **DDEF Values in Non-pregnant and Pregnant Human Cohorts Are the Same.**
The results of the Population analysis across simulated cohorts of non-pregnant and pregnant women are then shown in Figure 2 below. The overall dose-response for these cohorts are quite comparable.

**Section 7 Figure 2.** Dose-response of peak RBC cholinesterase inhibition in simulated cohorts of non-pregnant women and pregnant women (n=10,000 per lifestage) following oral or dermal exposure to chlorpyrifos. Note average female values for non-pregnant and pregnant women (Figure 1) are overlaid on individual value “cloud” output (data from Poet 2015).
Dow AgroSciences LLC  
Study ID: GRO4302015  
Page 73

Percentile analysis of the Population model output affords DDEF values for adult humans (male+female), and non-pregnant and pregnant women. As shown in Table 1 the DDEF values for non-pregnant and pregnant women are both comparable (3.5-4.0). Also, the variation in RBC POD response calculated for a non-pregnant population (3.5) is less than a male/female adult population (3.7-4.1).

Section 7 Table 1. Estimates of DDEFH for chlorpyrifos in pregnant and non-pregnant women following oral or dermal exposures (data from Poet 2015).

<table>
<thead>
<tr>
<th>DDEF</th>
<th>Male and Female</th>
<th>Non-Pregnant Female</th>
<th>Pregnant Female‡</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>POD&lt;sub&gt;SH&lt;/sub&gt; (5&lt;sup&gt;th&lt;/sup&gt; percentile)</td>
<td>POD&lt;sub&gt;SH&lt;/sub&gt; (1&lt;sup&gt;st&lt;/sup&gt; percentile)</td>
<td>POD&lt;sub&gt;SH&lt;/sub&gt; (5&lt;sup&gt;th&lt;/sup&gt; percentile)</td>
</tr>
<tr>
<td>Oral</td>
<td>2.7</td>
<td>4.1</td>
<td>2.5</td>
</tr>
<tr>
<td>Dermal</td>
<td>2.7</td>
<td>3.7</td>
<td>2.7</td>
</tr>
</tbody>
</table>

‡ pregnant cohort for oral is 3<sup>rd</sup> and dermal is 2<sup>nd</sup>, based on most sensitive group.

In conclusion, the well-validated PBPK/PD model was expanded to include prediction of systemic exposure and RBC cholinesterase inhibition in pregnant women. Analysis of the dose-response for non-pregnant and pregnant women showed comparable POD values for the three exposure routes of oral, dermal and inhalation. A more comprehensive analysis of the variation in the RBC POD across populations of non-pregnant and pregnant women afforded comparable DDEF values between these lifestages. Based on these results from the updated PBPK/PD model, it is apparent that the existing DDEF intraspecies uncertainty value of 4x for humans across lifestages is also appropriate for pregnant women.

7.5. In Utero Exposure/Sensitivity Studies Show No Additional Sensitivity for Fetuses.

While the results of the PBPK/PD model show that the RBC DDEF of 4x is appropriate for pregnant women, it is also important to understand the relative exposure and probable RBC POD to the human fetus in utero.

Well-conducted studies have shown that fetuses are not more sensitive to CPF exposures than dams. The effects of chlorpyrifos (CPF) on fetuses were described in Mattsson et al. (2000). Pregnant dams were exposed daily from gestation day (GD) 6 – lactation day (LD) 10 with CPF via gavage at doses of 0,0.5, 1.0, 5.0 and 10 mg/kg/day (sperm positive = GD 0). On GD 20, dam and fetal samples were collected at 4 h after gavage administration, the time of maximum CPF exposure in blood. Five dams were evaluated for CPF toxicokinetics (TK) and 5 dams were analyzed for cholinesterase (ChE)
inhibition. For fetuses, five males and five females/dose group, each from different litters, were evaluated for chlorpyrifos TK. The same sampling strategy was used for fetal ChE samples (five males and five females/group, each from different litters).

CPF was readily detected in the blood of high-dosage dams when measured 4 h after dose administration (108.8 ng/g blood). CPF also was detected in the blood of mid-dosage dams on GD 20 (2.6 ng/g), but was not measurable in low-dose dams. Blood CPF levels in high- and mid-dose fetuses (males and females combined) on GD 20 were 46.1 and 1.1 ng/g, respectively. These blood CPF data show that fetuses have a lower exposure than their dams, with blood levels 2-3 less than in dams.

In high-dose dams (5 mg/kg/day), ChE was markedly inhibited in all tissues (brain, heart, plasma, RBCs). At the mid-dosage level (1 mg/kg/day), tissues exhibited the following sensitivity to ChE inhibition: RBC ≈ plasma ≥ heart > brain (least inhibited). Low-dose dams (0.3 mg/kg/day) had significant inhibition of plasma and RBC ChE. In contrast, no ChE inhibition was seen at the low or mid-dose levels in fetuses. Only at the high-dose of 5 mg/kg/day was ChE inhibition seen in fetuses, with the magnitude of response less than dams in all 5 tissues studied.

In general then, in a well-designed study to measure both systemic exposure and ChE effects in pregnant rats, fetuses had systemic exposures 2-3 fold lower than dams, with corresponding lesser ChE inhibition. Similar findings for repeated maternal dosing have been reported by Chanda and Pope (1996) and Lassiter et al. (1998). Together, these data indicate that GD 20 fetuses are less sensitive to CPF-induced ChE inhibition than their dams. These animal systemic exposure data are also quite consistent with reported fetal:maternal exposures in a human cohort study, in which the highest exposure fetal cord blood levels were found to be 2-3 fold lower than the corresponding maternal levels (Whyatt et al. 2004).

SECTION 7 REFERENCES


8. EPA’S USE OF THE COLUMBIA AND OTHER EPIDEMIOLOGY STUDIES TO BASE ITS RISK ASSESSMENT CONCLUSIONS IS NOT SCIENTIFICALLY SUPPORTED.

Summary:

- EPA relies upon an unreplicated study, the Columbia Study, which is contrary to standards for data reliability and sets a poor standard for regulatory decision making. Adverse results reported in the Columbia Study are not found in other populations. Multiple reviews concluded that at the measured levels of exposure, the evidence from the epidemiology studies is insufficient to show causality between chlorpyrifos and adverse neurodevelopmental effects in infants and children.
- The analytical method used in the Columbia Study has not been validated at the low concentrations reported in blood.
- The Weight of Evidence analysis in the RHHRA is not properly executed according to scientific standards and is characterized by accumulating a list of positive findings in the absence of a mode of action for purported neurodevelopmental findings in humans.
- There is no standard or process to insure transparency of both positive and negative results for epidemiology results in RHHRA. Validation of epidemiology results should be a criterion for their use in human health risk assessment.
- Decision making regarding epidemiology in the RHHRA is qualitative and lacks scientific vigor.
- The epidemiology study results for the Mt. Sinai and Columbia Studies are based on outdated use patterns from more than 15 years ago. EPA has already succeeded in reducing exposures to pregnant women and children.

8.1. EPA Relies Upon an Unreplicated Study, the Columbia Study.

The Columbia Study forms the basis for the Agency’s conclusions in the RHHRA. The key outcomes evaluated over 10 years of observation of the study cohort include fetal growth, neonatal neurological function, mental and psychomotor development, attention problems, intelligence and brain imaging (Rauh et al. 2004, Whyatt et al. 2004, Rauh et al. 2006, Rauh et al. 2011, Rauh et al. 2012). All findings were correlated with a single in utero exposure estimate from chlorpyrifos levels in cord blood or maternal blood at delivery.

The RHHRA fails to recognize that no epidemiologist can replicate the Columbia Study because the exposure circumstances among the participants no longer exist in the U.S. Chlorpyrifos exposure to the mothers in the Columbia Study was assumed to have incurred from repeated chlorpyrifos applications to control pests in their inner city residence. More than 2/3 of the chlorpyrifos samples were collected prior to 2001, when urban uses of chlorpyrifos were registered. These uses no longer exist in the U.S. To
replicate the Columbia Study, another cohort of exposed women is required. Pregnant farm women would not constitute a valid or feasible cohort for comparison to the potential exposure patterns in the Columbia Study. EPA has concluded potential bystander exposure from volatilization does not present a risk to human health. Further agricultural uses tend to be more seasonal and episodic plus farm spouses have been shown to have little exposure from drift (Alexander et al. 2006). The inability to replicate the Columbia Study underscores the importance for access to the underlying data to permit other investigators to independently evaluate the multiple exposure scenarios, the health outcomes over time, and explore sensitivity of analytical assumptions. An analogous example was discussed by two epidemiology journal editors (Hernan et al. 2009). We learned in the RHHRA that the data from the Columbia Study enrollment questionnaire was “deemed of such poor quality . . . that the data were not coded or entered into the analytic data file.” RHHRA at 387. Questions then exist as to: Why are these data so poor? What is the quality of the other data collected? Does this information quality permeate in other responses from the cohort? How can EPA justify using results for risk assessment?

The Agency recognized and reviewed two other similarly designed prospective children’s health cohorts in their summary of epidemiology findings: the Mt. Sinai Children’s Health and Development Study (Mt. Sinai) and Center for Health Assessment of Mothers and Children of Salinas Valley (CHAMACOS, Berkeley study). RHHRA at 223. Whereas the Agency suggested that their findings “bolster” the observations of the Columbia Study, RHHRA at 40, multiple reviews in the peer reviewed scientific literature disagree and describe the evidence as inadequate, inconsistent and implausible (Needham 2005, Zhao et al. 2005, Eaton et al. 2008, Prueitt et al. 2011, Li et al. 2012, Mink et al. 2012, Burns et al. 2013). We agree that the three cohorts share common strengths in design, but also share significant limitations inherent with evaluating multiple exposures and multiple health outcomes. Independent replication in other populations is required since all human observational studies are subject to limitations.

8.2. The Columbia Study has Several Key Limitations which Diminishes its Validity Standing Alone.

These limitations have been discussed in a paper by Edwards et al. (2014) that has been previously submitted to the Agency and are incorporated herein by reference.

8.2.1. The Analytical Method Used in the Columbia Study Has Not Been Validated at the Low Concentrations Reported in the Blood.

Because a majority of samples from the Columbia cohort are below the validated limit of detection (LOD) for chlorpyrifos analysis in plasma/serum, the conclusions regarding outcomes and
associated exposure based on chlorpyrifos levels < 15 picograms (pg)/gram (g) are not reliable. This impacts the reliability of the correlation analyses between exposures and most outcomes since the study dichotomized exposure as “low” and “high” using 6.17 pg/g as its cut point (Whyatt et al. 2004, Rauh et al. 2006). When all values are used in linear analyses, such as when evaluating IQ (Rauh et al. 2011), there may be substantial misclassification of exposure. Access to the raw data would permit additional sensitivity analyses to understand impact to the risk estimate.

It is a basic foundation of the scientific process that researchers must show that a quantitative exposure measurement is accurate, precise, and reproducible across the range of values determined within a study. For example, the USEPA method validation guidelines call for replicate determinations of analyte recovery from a given matrix (substrate) down to the stated LOD (USEPA 1998). However, this has not occurred within the Columbia Study. There were no data generated during validation of the plasma/serum analysis method (Barr et al. 2002) or during the subsequent analysis of the Columbia cohort samples to show that chlorpyrifos levels could be accurately measured in plasma/serum matrix down to the stated LOD of 0.5-1 pg/g (note: authors use LOD term when discussing limit of quantitation). The lowest concentration for which analyte recovery in plasma/serum was determined using this method was 15 pg/g. This is a critical point, as more than 80% of the Columbia subjects had levels below this validation level. Further, there was no evaluation of possible sample contamination during blood collection in the hospital, processing to plasma, or during shipment to the CDC. Analysis of sample integrity is a critical parameter of all biomonitoring studies, especially those at the trace levels reported for this cohort. Note that Barr et al. (2002) also reported background chlorpyrifos levels of 9 pg/g in control serum samples, 50% higher than the “high” exposure Columbia cohort criteria, the source of which was never determined. Finally, the CDC has stated that chlorpyrifos blood measurements from the 2003-2004 NHANES survey will not be released because the CDC lab was not able to meet its own QC/QA (Quality Control/Quality Assurance) criteria for the assay (personal communication, CDC). This is the same method used in the Columbia Study, so any decisions based on the use of such methodology should be highly scrutinized.

8.2.2. There are Credible Alternative Explanations for the Neurodevelopmental Effects Observed in the Columbia Study.

Chlorpyrifos cannot reliably be deemed a causal factor for the neurodevelopmental effects reported by the Columbia researchers. Alternative explanations are credible and present themselves logically when considering exposure measurement error. The mothers and children within the Columbia
Study who had measurable exposures to chlorpyrifos were also exposed to other chemicals that have the potential to subtly or profoundly affect child neurodevelopment.

Poverty and pesticide exposure are highly correlated. Mothers and children who live in crowded, substandard housing have been found to be more likely to encounter exposure to multiple and heavily applied pesticides, both legal and illegal (e.g., Morbidity and Mortality Weekly, 1997). Indeed, a survey of the Columbia cohort indicated that pesticide use was frequent (Whyatt et al. 2002). It has been proposed that insecticide exposure (regardless of the chemical) may be a marker for insect infestation (and other related factors) and may not itself be the causal agent driving the neurodevelopmental results (Burns et al. 2013). In fact, the Columbia authors reported an association with the Bayley Scales of Infant Development (BSID) and piperonyl butoxide, a synergist used with pyrethrins and synthetic pyrethroid insecticides, which replaced the use of chlorpyrifos in residential settings after 2001 (Horton et al. 2011).

It is well documented in the literature that social hardships related to poverty and maternal depression can affect scores on intelligence tests and other measures of cognitive ability (e.g., Luby et al. 2013; Duncan et al. 1997; Feinstein, 2003; Canadian Pediatric Society, 2004; Center on the Developing Child at Harvard University, 2009, Rauh, et al., 2004). In the Columbia Study (Rauh et al. 2006), neurodevelopmental effects were only observed at 3 years of age, not before. As the children age from birth to 3 years, there are a number of other well-known nonchemical risk factors that affect brain development. Efforts were made by the Columbia Study investigators to account for certain risk factors, including the influence of race/ethnicity, gestational age, maternal education and maternal IQ (albeit, there were missing IQ data for several dozen women in the study). Observational data on the quality of the home care-taking environment were also considered, but it is unclear to what extent key risk factors were addressed. For example, information was collected on mothers’ feelings and state of mind but there is no indication that these potential risk factors were explicitly addressed. Interestingly, maternal depression was a significant factor for influencing childhood behavior, as modeled by the UC Berkeley investigators (Eskenazi et al. 2007, Marks et al. 2010).

Despite efforts made by the Columbia Study investigators to account for other risk factors, the influences of other chemical and nonchemical stressors which could contribute to or account for the observed associations of impaired neurodevelopment cannot easily be attributed to the independent effects of a single chemical (i.e., chlorpyrifos) in the multi-chemical exposure scenario experienced by the Columbia cohort, particularly spanning a multi-year period that encompasses an important period of sequential neurodevelopment (e.g., SAP, 2012; Eaton et al. 2008). Any inferences based on the Columbia Study regarding the degree to which chlorpyrifos contributes to the measured outcomes cannot
be separated easily from other risk factors, and thus the study cannot be used to reliably address the question of whether chlorpyrifos can cause neurodevelopmental effects at the exposure levels reported. Although it is legitimate for academic scientists to propose and investigate hypotheses, the Columbia Study cannot serve as a reliable basis for addressing key questions regarding a single chemical in a regulatory risk assessment.

8.2.3. Measurements in the Columbia Study Do Not Reflect Exposure Over Time.

Another significant limitation of the Columbia Study relates to the exposure data, *i.e.*, measurements of chlorpyrifos do not reflect exposure over time. Evaluations of neurodevelopmental scores/function on the cohort continued into childhood and early adolescence, which is well beyond the single snapshot in time of chlorpyrifos measurement. This is especially pertinent since neurodevelopment occurs both prenatally and postnatally, essentially a continuous process throughout early infant and childhood years (*Selevan et al.* 2000). The Columbia Study focused exclusively on prenatal exposure as measured by cord/maternal blood measures of chlorpyrifos within two days of birth. Furthermore, the maternal and cord blood measurements represent a single sample, or snapshot (*i.e.*, only one point in time), collected for convenience (at birth) and with no information regarding the chlorpyrifos home application. Given the rapid metabolism of chlorpyrifos in humans and subsequent short residence time in the body, a single sample obtained at the time of delivery or shortly after would have little relationship or meaning to exposure levels that were present during most of the pregnancy (or thereafter). Also, as discussed earlier, the chlorpyrifos blood measurements cannot be deemed accurate. The inadequate investigation on exposures to either chlorpyrifos or other pesticides and chemicals (*e.g.*, polycyclic aromatic hydrocarbons, lead, etc.) results in an incomplete exposure picture.

8.2.4. Adverse Results Reported in the Columbia Study Are Not Found in Other Populations.

Multiple reviews concluded that at the measured levels of exposure, the evidence from the epidemiology studies is insufficient to show causality between chlorpyrifos and adverse neurodevelopmental effects in infants and children. An important aspect of determining the validity of an epidemiology study is whether findings can be reproduced; that is, associations between similar outcomes and exposures to the chemical of interest should be found in different populations. Chlorpyrifos is measured in different ways across studies, with some measuring chlorpyrifos itself, and others measuring other biomarkers that represent exposure to chlorpyrifos and other chemicals, such that exposure to chlorpyrifos itself cannot be teased out. The order of reliability of biomarkers is as follows: chlorpyrifos > 3,5,6-trichloro-2-pyridinol (TCPy) > diethylphosphates (DEPs). The metabolite DEP can reflect
exposure to pesticides other than chlorpyrifos. TCPy and DEPs in urine can also result from exposure to these OP metabolites in food or the environment rather than to chlorpyrifos or other OPs. Importantly, the nonspecific metabolite of all organophosphates, dialkylphosphate (DAP) does NOT indicate exposure to chlorpyrifos.

When considering the order of reliability of biomarkers, the results of other epidemiology studies do not implicate chlorpyrifos. Specifically, the Mt. Sinai study and the CHAMACOS study do not confirm the results reported by the Columbia researchers (Eaton et al. 2008; Prueitt et al. 2011; Li et al. 2012; Burns et al. 2013). Outcomes evaluated with the most specific biomarker, urinary TCPy, are either not statistically significantly correlated with any health outcome or are not analyzed by investigators at Mt. Sinai (Berkowitz et al. 2004, Engel et al. 2007) and CHAMACOS (Eskenazi et al. 2004, Eskenazi et al. 2007, Marks et al. 2010, Bouchard et al. 2011).

Further, there are two additional epidemiology studies (not discussed by the Agency) that have not observed consistent associations with birth weight or developmental outcomes. These studies measured chlorpyrifos (cord blood) or urinary TCPy with reported exposure levels higher than or comparable to the Columbia or CHAMACOS studies (Fortenberry et al. 2012, Wickerham et al. 2012). Although these studies did not investigate all of the outcomes measured in the Columbia Study, findings for endpoints that were evaluated do not confirm findings from the Columbia Study (Rauh et al. 2006 and 2011; Whyatt et al. 2004). Based on epidemiological data published through 2007, Eaton et al. (2008) also concluded that there were no consistent associations observed when neurodevelopmental outcomes of the Columbia, Mt. Sinai, and CHAMACOS studies were compared.

8.3. EPA’s Weight of Evidence Analysis is Poorly Executed and is Characterized by Accumulating a List of Positive Findings in the Absence of a Mode of Action.

Additional examination of a Weight of Evidence analysis is provided in comments submitted to the docket by Gradient Consulting (submitted to docket: EPA-HQ-OPP-0850; April 2015).

According to Section 4.6 Weight of Evidence Analysis and Appendix 2 (Detailed review and synthesis of three children’s environmental health cohort studies)) in the RHHRA, the Agency considered strength of the association, exposure-response, temporality and alternative explanations in their evaluation of the epidemiology data. The EPA does not discuss biological plausibility. It is troubling that the Agency cannot establish a mode of action of the neurodevelopmental outcomes reported in the epidemiology literature. The Agency does recognize that the exposures in the epidemiology study subjects were unlikely to result in AChE inhibition. RHHRA at 45.
Strength. The Agency considers some apparent associations between possible exposures and claimed effects as “strong” but does not define precision or the meaning of “strong.” For example, the Agency discusses the “relation of mental and psychomotor development among toddlers (Bayley Scale for 24 – 36 months) with prenatal chlorpyrifos exposure is elevated approximately 2 – to 4 – fold among those more highly exposed.” RHHRA at 245, RHHRA at 245. These associations are statistically significant which suggests precision and risk estimates above 2, which suggests strength. However, the CHAMACOS and Mt. Sinai studies reported beta-coefficients which were not statistically significant for maternal TCPy and DEP. Further, the CHAMACOS study reported statistically significantly better performance on these tests when using the child DEP. These results are neither strong nor precise. Whereas the Agency considers these results to bolster those of the Columbia Study, this was not the conclusion in published reviews (Prueitt et al. 2011, Li et al. 2012, Burns et al. 2013). One of the peer reviewed summaries of the epidemiology data cautions “against simply accumulating a list of positive, statistically significant, yet potentially random findings,” which is what the Agency seems to have done (Li et al. 2012).

Exposure-response. There is little evidence of increasing effect with increasing dose in the three available cohorts. Many analyses relied upon high vs. low dichotomous exposure classification and did not evaluate a trend. Further, the EPA fails to discuss how bias can be introduced in setting arbitrary cut off values with no biological basis. Some of the published analyses evaluated departures from linearity when using continuous data. However, the actual results were not shown. This is an example where availability of the underlying data of all the studies would permit additional analyses.

Temporality. The Agency correctly concludes that the measured chlorpyrifos exposure precedes the observed health effects in the three cohort studies. However, as noted above, the investigators collected no exposure information from the developing child. Therefore, the investigators, and the Agency, cannot rule out that other etiologic important factors occurred after birth, and after the measured chlorpyrifos exposure.

Alternative explanations. On RHHRA at 248, the Agency dismisses alternative explanation. They assume but have not demonstrated that errors would lead to underestimation of the true association. This is a naïve assumption that is discussed in Epidemiology textbooks that occurs only under specific circumstances (Gustafson, 2004; Rothman et al. 2008). The fact that misclassification of exposure can result in biased results is similarly discussed in a recent publication by EPA epidemiologists (Christensen
et al. 2015). In the RHHRA, the Agency does suggest that other pesticides may be involved. However, they do not fully discuss other possible co-exposures related to poverty or genetic factors in these unique populations.

The Agency uses lack of statistical significance in birth weight in Columbia infants born after 1/1/01 as evidence of a “prevented” association (Whyatt et al. 2004). RHHRA at 247. Importantly, the Columbia authors do not reveal actual mean birth weights but only beta-coefficients and p-values. Further, in their response to the Agency and SAP, Columbia investigators Drs. Whyatt and Rauh (2011) explained [on difference in birth weights in infants born after 1/1/01], “that there was only one child with high (group 4) chlorpyrifos exposure in this post-ban sample, it is not surprising that there was no significant difference in birth weight between the <LOD group and the small group with some exposure during this post-ban period.” RHHRA at 258. This means that there was no heterogeneity of exposure, precluding meaningful interpretation of statistical testing for birth weight.

In a letter to the editor regarding Columbia’s Rauh et al. (2006) paper, Cicchetti notes that the high and low exposure groups varied dramatically in characteristics that would also be related to developmental scores (Cicchetti 2007). Cicchetti suggests that confounding by race, ethnicity, income and other factors related to the home environment is important. Indeed, in another publication on the New York City birth cohort in the Columbia Study, material hardship, defined as “unmet needs” in food, housing, and clothing were negatively associated with cognitive development (Rauh et al. 2004). This relationship demonstrates that other factors are related to neurodevelopment in this urban population. Since the levels of chlorpyrifos reported in cord blood were highly correlated with the presence of a number of other pesticides such as diazinon, dicloran, 2-isopropoxyphenol, and tetrahydrophthalimide (Whyatt et al. 2003), the conclusions regarding chlorpyrifos may be confounded by complex environmental or maternal factors. Is, for instance, chlorpyrifos an index for pest infestations rather than a toxic exposure? Further, by not collecting any behavioral or exposure information on the developing child, the investigators cannot evaluate other confounding exposures, such as that of lead.

Further, the co-factors of ethnicity (language), gestational age, maternal education (low), and HOME score were increasingly significant from 12 to 36 months. The Agency fails to discuss the low R^2 for the regression models (10 – 25%) in the analyses reported both by Rauh et al. (2004) and Lovasi et al. (2011). This indicates that the variability of the Mental Development Index (MDI) and Psychomotor Development Index (PDI) score are poorly explained, even with statically significant covariates such as chlorpyrifos. These factors suggest that analyses for chlorpyrifos alone are not indicative either of the range of chemical exposures or of other factors potentially influencing development among the study participants.
subjects. With a complex dataset, the role of confounding can be more important than the exposure of interest.

8.4. All Epidemiology Studies Relied Upon by EPA Are Marked by a Lack of Transparency and No Underlying Raw Data.

Transparency and documentation of the decision process are at the core of a scientifically-sound, credible risk assessment. EPA’s Office of Pesticide Programs has a long history of transparency as well as data disclosure in risk assessments to ensure the credibility of its registration and reevaluation decisions. OPP’s transparency in its risk assessments and decision-making adheres to President Barack Obama’s January 21, 2009 Memorandum to Heads of Executive Departments and Agencies on “Transparency and Open Government” (Obama, 2009). Given the concerns about the reliability of exposure assessment in the Columbia Study, there would be scientific value in accessing the data for the purposes of exposure (dose) reconstruction and review of the health effect analyses. Similarly, the UC Berkeley CHAMACOS and Mt. Sinai studies (Eskenazi et al. 2007; Marks et al. 2010; Bouchard et al. 2011; Engel et al. 2011) conducted no health analyses using chlorpyrifos in cord blood or with urinary TCPy after age two. Access to and independent analyses of these data would also be informative to determine the scientific reliability of the Columbia results.

The EPA has indicated publicly, “The studies that are the most relevant and informative to risk assessment are those that clearly and fully describe study design, conduct and methods, as well as providing access to the underlying data.” (http://www.epa.gov/pesticides/science/literature-studies.html). OPP has considered the Columbia Study, which is a federally funded study, as a source of data intended for consideration in its chlorpyrifos risk assessment (see SAP 2008; 2012). Independent verification of the analyses and the ability to answer specific questions regarding the Columbia Study (e.g., other risk factors, an evaluation of different cutoff points for exposure and health outcomes) are not possible. This lack of access is counter to the recent February 22, 2013 John P. Holdren Memorandum to Heads of Executive Departments and Agencies on “Increasing Access to the Results of Federally Funded Scientific Research.” (Holdren, 2013). Thus, any significant cited line of evidence in EPA’s chlorpyrifos risk assessment should be based on accessible data sets that allow for independent analysis and verification of conclusions. We acknowledge the importance of protecting the privacy of the subjects in epidemiology studies, but there are well-recognized and accepted ways to provide data on cohort subjects while protecting the privacy of the subjects. Given the problems and complex issues involved with the chlorpyrifos cohort data, including the type of cognitive assessment used, a more thorough and multidisciplinary scientific review is needed, which provides some access to the data and includes
pediatricians, epidemiologists, clinicians and neuropsychologists experienced in evaluation of pediatric cognitive function.

8.5. **There is No Standard or Process Used to Insure Transparency and Validation of the Epidemiology Study Results.**

As discussed earlier, the Columbia investigators are unwilling to share their raw data with the Agency. RHHRA App. 6. In addition, the CHAMACOS study measured parent chlorpyrifos in cord blood and maternal TCPy in urine, but neither has been fully evaluated and reported. As shown in the Agency summary of findings Table 1 of the RHHRA, the CHAMACOS investigators have not reported analyses using chlorpyrifos in cord blood for any health outcome, and only reported analyses using urinary TCPy for fetal outcomes. RHHRA at 228. This represents a reporting bias on the part of the investigators by not reporting all results. Industry is held accountable to full reporting of all observations that indicate harm (FIFRA Section 6(a)(2), Section 8(e) of Toxic Substances Control Act, 15 U.S.C. Section 2607(e)). If EPA believes that an epidemiology study such as the Columbia and CHAMACOS studies are critical to an evaluation of chlorpyrifos hazard and potential risk, then all data should be requested by the Agency, both positive and negative for a given study. Both are critical for weight of the evidence decision-making.

- The authors of the primary epidemiology study under EPA’s consideration in this draft assessment (i.e., from Columbia University) have consistently refused to make their raw data available for the inspection and independent evaluation by EPA scientists so that EPA can assess its reliability.
- The Agency has not sought access to the raw data for the other two cohort studies which it considers “bolster” the results from Columbia.
- In contrast, registrants are required to share their raw data with EPA and be able to demonstrate that Good Laboratory Practices have been used throughout in the conduct of their studies.
- Analyses of epidemiology data were reported in peer reviewed journals, not for risk assessment. There are additional analyses related to bias, confounding, impact of categorization of exposure, tests for linearity, and not the least of which, exposure assessment, which could be informative to the Agency if they had access to the underlying data from each publication.

8.6. **Decision-Making Regarding Epidemiology is Qualitative and Lacks Scientific Rigor.**

In their review of epidemiology studies in mothers and children, the Agency considered the Columbia Study results to be the more “relevant,” with the other two cohorts providing “supporting
information.” RHHRA at 32. However, the review is not fully robust and is seemingly based upon conclusions believed to be, but instead should be based on standards of scientific rigor.

- Page 33, the EPA “believes that random or systematic errors in the design, conduct or analysis of these studies were unlikely to fully explain observed positive associations between in utero chlorpyrifos exposure and adverse neurodevelopmental effects.” (emphasis added).
- Page 43, the “EPA believes that it is more likely that research results were under-estimated, rather than over estimated.” (emphasis added).
- Page 43: “EPA believes that authors were able to appropriately measure and model the effect of environmental exposures on the study outcomes.” (emphasis added).
- Page 244, “the EPA believes the possibility of under-estimation of effect size is more likely than factors that would lead to over-estimation of effect size.” (emphasis added).

These beliefs are not supported with scientific rigor by the Agency. For example, repeatedly, the Agency assumes bias is non-differential, i.e., not related to health outcome, because of the prospective design of the studies. However, this common assumption was discussed by approximately 30 epidemiologists at a workshop during which they recommended that uncertainty in exposure estimates be quantified and the direction of the effect demonstrated (Burns et al. 2014). In fact, the direction of the effect size is not always under-estimated, particularly when the exposure is polytomous or other variables are also misclassified (Thomas 1995, Jurek et al. 2008, Gustafson 2004, Rothman et al. 2008).

8.7. The Epidemiology Study Results are Based on Outdated Use Patterns From More Than Fifteen Years Ago.

The three prospective epidemiology studies all began enrollment of pregnant women in 1998. By 2001, U.S. registration of indoor uses of chlorpyrifos was withdrawn. The Columbia Study was still enrolling participants in 2001 and 2002. The Agency’s interpretation of the association of the epidemiology health effects and chlorpyrifos levels are based upon use patterns which have already been mitigated. Several publications from Columbia demonstrate low to nondetectable chlorpyrifos levels in the pregnant women enrolled after 2000. Another study that collected chlorpyrifos in cord blood similarly confirmed the lack of indoor exposure after 2000 (Yan et al. 2009).

The source of chlorpyrifos in the CHAMACOS study could be related to agricultural uses since ~26 – 28% of the women were employed in agriculture while pregnant. (Eskenazi et al. 2004, Huen et al. 2012). However, none of the agricultural related determinants (i.e., whether the mother worked in agriculture, lived with an agriculture worker, or lived near a field during pregnancy) were associated with
chlorpyrifos levels in mothers or their newborns (Huen et al. 2012). These facts related to exposure should be considered and discussed by the EPA.

The Agency provides no discussion about exposure to children, despite incorporating FQPA safety factors related to childhood exposure. It is important to note that there is evidence of minimal early life exposure to the Columbia Study children (Whyatt et al. 2009). Other studies that did evaluate chlorpyrifos (or organophosphate) exposure in children have found evidence of no adverse effects. The CHAMACOS study reported improved performance on development at 12 - 24 months based on several analyses using the child’s urine (Eskenazi et al. 2007). The investigators reported the children with higher organophosphate exposures performed better on their mental development (MDI) tests (Eskenazi et al. 2007). Study researchers offered anecdotes that are related to exploring behavior and better diet to explain the association. A recently reported study in Thailand similarly reported that chlorpyrifos exposure (as measured in the children’s urine) was not a significant predictor of adverse neurobehavior performance among children aged 6 -8 (Fiedler et al. 2015). This directional shift supports the alternative hypothesis that at population levels of exposure there is no adverse effect in children.

8.8. In Conclusion, the Epidemiology Data are Not Sufficiently Robust to Support the Hypothesis that Chlorpyrifos is a Causal Factor in Neurodevelopmental Effects.

Whereas the Columbia cohort results were based on a robust exposure measure, chlorpyrifos in blood, one cannot rule out false positive results because of lack of replication, uncontrolled or unmeasured confounding, and potential exposure misclassification. We agree with the Agency recommendation to place “higher confidence in results which are replicated or reproduced from multiple studies” (US EPA, 2010). The adverse health effects reported in studies of the Columbia cohort have not been adequately replicated elsewhere. With respect to exposure, the Agency relies upon associations of urinary DAP and health outcomes in the CHAMACOS and Mt. Sinai studies to support the results of the Columbia Study, ignoring the lack of significant correlations for maternal TCPy (a metabolite of chlorpyrifos) and DEP (more specific than DAP) reported for CHAMACOS and Mt. Sinai (Eskenazi et al. 2007, Engel et al. 2011). Results from the Columbia Study reported statistically significant inverse association between chlorpyrifos (as estimated from cord blood) and full-scale intelligence quotient (FSIQ) (Rauh et al. 2011). Neither the CHAMACOS nor Mt. Sinai studies identified statistically significant analyses of diethylphosphates, a metabolite of chlorpyrifos (as measured from maternal urine during pregnancy) and FSIQ (Rauh et al. 2011). Several peer reviewed publications have carefully reviewed the epidemiology data for consistency across the three studies. Mink et al. (2012) in reviewing the birth outcomes reported “no notable or consistent patterns of association across the different cohort
studies.” Li et al. (2012) concluded there were “no consistent patterns of adverse association across studies.” In a hypothesis based weight of evidence, Prueitt et al. (2011) also concluded “many inconsistencies in the results both within and among the cohort studies examining the association between chlorpyrifos exposure and neurodevelopmental outcomes in newborns and young children. . . . Overall, the epidemiology data are not sufficiently robust to support the hypothesis that chlorpyrifos is a causal factor in neurodevelopmental effects.”

Section 8 References


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


Luby et al., 2013; Duncan and Brooks-Gunn, 1997; Feinstein, 2003; Canadian Paediatric Society, 2004; center on the Developing Child at Harvard University, 2009.


9. **OCCUPATIONAL MIXER/LOADER/APPLICATOR/FLAGGER FOR CROPS, NON-CROPS AND SEEDS & REI**

**Summary:**

- The Level of Concern (“LOC”) should be reduced to 4 based on the use of new PBPK modeling to support an intraspecies uncertainty factor of 4X along with a more scientifically justified FQPA Safety Factor of 1X. With the LOC of 4, all current occupational use scenarios would meet the acceptable risk standard with the PPE/Engineering Controls, Use Rates, and Restricted Entry Intervals (“REI”) on current Dow AgroSciences’ labels.

- Use of PBPK modeling can be extended to allow consideration of any exposure duration to develop an appropriate PoD and this would allow further refinement of for crop- and use-specific risk assessments.

- In all cases, the Pre-Harvest Interval (“PHI”) is protective of the REI for hand harvesting activities on DAS labels, as the PHI on the current labels already exceed the REI proposed in the RHHRA.

- For some crops, incorrect transfer coefficients were used in the RHHRA Occupational Assessment.

- PPE for Airblast Applications: Chlorpyrifos labels require chemical resistant headgear for overhead applications which is not taken into account in the RHHRA Occupational Assessment.

- Further refinement of the aerial application scenarios can be done to better simulate real-world practices.

9.1. **Occupational Risk Assessment Safety and Uncertainty Factors Should Result in LOC of 4.**

The trigger for whether an occupational use scenario is considered acceptable is when the Margin of Exposure (“MOE”) exceeds the LOC. The MOE is calculated as the toxicological or hazard endpoint, such as NOAEL or Point of Departure (“PoD”), divided by the estimated exposure. The LOC is determined by multiplying the Uncertainty and Safety Factors (“UF” and “SF”). The LOC for occupational exposures to chlorpyrifos proposed in the RHHRA is 100, based on a 10X SF for FQPA concerns and an intraspecies uncertainty factor of 10X for women during pregnancy.

The reset of the FQPA SF to 10X based on the epidemiology studies, and most specifically the Columbia Study, is inappropriate (as discussed in Sections 5, 6 and 8) and significantly over-inflates the number of occupational use scenarios that do not pass the EPA RHHRA assessment. In addition, PBPK modeling (Section 7) shows that the intraspecies UF of 4X for male and female adults is also protective of pregnant women in occupational settings. Therefore, the LOC for occupational exposures to chlorpyrifos should be 4 (FQPA 1X x intraspecies UF 4X) which will have a significant impact on conclusions based on the outcome of the occupational assessments.
In the RHHRA, EPA starts with a dermal PoD of 3.63 mg/kg/day from PBPK modeling of 10% RBC ChE inhibition for human females. Factoring in the current LOC of 100, the maximum acceptable dermal exposure in the RHHRA is 0.036 mg/kg/day. With reduction of the FQPA SF to 1X and reduction in the intraspecies UF to 4X, the LOC is 4 and the final maximum acceptable dermal exposure would be 0.91 mg/kg/day, or about 25 times higher.

With the changes to the Safety and Uncertainty Factors described above resulting in a LOC of 4, all current occupational uses scenarios would be considered as meeting the acceptable risk standard with the PPE/EC, use rates, and Re-entry Intervals (REI) on current DAS labels.

9.2. Occupational Handler Exposure Assessment: Overall Comment; Opportunities for Refinement

EPA utilized a PBPK model to develop a point-of-departure (POD) for occupational risk assessment based on an exposure duration assumption of 5 days/week for 3 weeks (Poet, 2015). In contrast to direct application of animal toxicology data, the PBPK/PD allows the user to consider any exposure duration (or exposure pattern) to develop PODs. Therefore, it is recommended that this PBPK model be utilized as an extra level of refinement for crop- and use-specific risk assessments. For example, crops and uses that have less frequent application days/week or fewer consecutive weeks of exposure can be utilized within the PBPK model to develop unique and specific PODs that most accurately reflect these particular uses. Additional evaluations of these alternative exposure scenarios are contained in comments to the docket submitted by Reiss (2015).

EPA has produced an extensive set of occupational handler exposure calculations. The results are summarized in Appendix F of the Occupational and Residential Exposure Assessment (D424484) and briefly reviewed in the RHHRA (D424485).

Due to the format of the results in the RHHRA, the risk for specific activities associated with specific crop uses is unclear. Further delineation of the following would allow a more thorough analysis of the various crop use scenario and occupational activities cited in the RHHRA as:

(1) the 132 of 285 scenarios where current label PPE are acceptable,
(2) the 27 scenarios requiring additional PPE or engineering controls, and
(3) the 126 scenarios that cannot be mitigated.

Additionally, EPA bundled “Crop or Target” entries for several crops/uses together when the application rate and acreage were the same. Although this approach results in fewer rows in the table,
bundling crops creates challenges when trying to identify which crops exceed the LOC and require mitigation. Furthermore, the fact that minimum PPE or engineering control specified on current labels is not indicated in the Agency’s assessment compounds the lack of clarity.

Such organization would make it possible to identify the PPE and/or engineering controls that would result in the greatest number of uses with MOE > LOC and would also allow for easier identification of those scenarios that present as MOE < LOC given current use patterns. If such improvements were used in the risk assessment the resultant increased transparency would be of significant use to facilitate further risk management decisions as chlorpyrifos continues through the registration review process.

9.3. Unit Exposures for Occupational Exposure Assessment

DAS identified an erratum in the occupational exposure assessment spreadsheet (provided by EPA), related to the dermal unit exposures (µg/lb ai).

Page 151, Table F.1 Chlorpyrifos Occupational Handler Non-Cancer Risk Estimates

1. Cell K79 (unit exposures (µg/lb ai), SL/G, M/L/A, L/SC/EC, Mechanically-pressurized Handgun, Ornamental Lawns and Turf, Sod Farms (Turf)): 390 should be 880. Using the incorrect dermal unit exposure of 390 µg/lb ai, the MAX MOE is 34, and with the correct dermal unit exposure of 880 µg/lb ai, the MAX MOE would be 30.

Page 158, Table F.2 Chlorpyrifos Occupational Handler Airblast Non-Cancer Risk Estimates

1. The header from the lower part of page 147 should be continued onto page 148 and then through the top of page 155. Additionally, the header from the top of page 147 should be included under the Flagger section on page 155. Additionally, on the bottom of page 155, the header from the top of Page 147 of 227 should start again. On page 151, the first 6 entries in Exposure Scenario 12g should read 1000 gallons, instead of 1000 square feet. Please note that, in the spreadsheet discussed above, the units are correct, i.e., 1000 gallons.

2. In Table F.2, the MOE for the “Engineering Control” scenario in the 4th row is listed as 1100, but the correct value is 130.

Page 159, Table F.2 Chlorpyrifos Occupational Handler Airblast Non-Cancer Risk Estimates

1. The MOEs listed under the scenarios “SL/G CRH PF5 R” and “DL/G CRH PF5 R” (i.e., the two middle MOE columns) are incorrect. The values listed are the same as those listed under “SL/G
CRH No R” and “D L/G CRH No R” in each row. The correct values for the “SL/G CRH PF5 R” and “DL/G CRH PF5 R” columns (organized by application rate and area treated) are shown below:

Corrected Total MOEs for Select Airblast Application Scenarios

<table>
<thead>
<tr>
<th>Application Rate (lb ai/A)</th>
<th>Area Treated (A/day)</th>
<th>Total MOE (LOC = 100)</th>
<th>SL/G CRH PF5 R</th>
<th>DL/G CRH PF5 R</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>40</td>
<td>4.4</td>
<td>4.3</td>
<td>6.3</td>
</tr>
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<td>40</td>
<td>6.1</td>
<td>8.8</td>
<td></td>
</tr>
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<td>40</td>
<td>6.5</td>
<td>9.4</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>1</td>
<td>40</td>
<td>26</td>
<td>38</td>
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</tbody>
</table>

9.4. Restricted Entry Intervals - Hand Harvesting Activities

Page 12, Par. 5

For the assessment of occupational post-application exposures, estimated risks indicate that no REI increase is required for the majority of outdoor environment crops and commodities with a labeled REI (i.e., 43 of 55 total). However, for 12 crops, activities such as irrigation, hand harvesting, scouting, and thinning result in risks of concern up to as many as 10 days following application.

In the case of hand harvesting, this activity would be limited by not only the labeled restricted entry interval (REI), but also the pre-harvest interval (PHI). In all cases, the PHI from the most recent (2014) chlorpyrifos master label exceeds the required REI for hand harvesting indicated in Table J.1 of the “Chlorpyrifos: Updated Occupational and Residential Exposure Assessment for Registration Review” (D424484), which indicates that hand harvesting would necessarily only occur outside of the required REI. The following crops are impacted by this:

- Strawberries: PHI = 21 days; REI for hand harvesting = 4 days.
- Cranberries: PHI = 60 days; REI for hand harvesting = 5 days.
- Field corn, Sweet corn: PHI = 21 days; REI for hand harvesting = 2-3 days.
- Cherries: PHI = 14 days; REI for hand harvesting = 1-5 days.
- Cole crops (broccoli, Brussels sprouts, cabbage, cauliflower, bok choy, collards, kale and kohlrabi): PHI = 21 days; REI for hand harvesting = 4-10 days.
9.5. Transfer Coefficients for Cabbage and Dormant or Delayed Dormant Tree Fruit

As listed in Appendix J of the RHHRA, for cole crops (broccoli, Brussels sprouts, cabbage, and cauliflower), a transfer coefficient of 4200 cm²/hr is used to assess exposure from post-application scouting activities. For cabbage, the recommended transfer coefficient for scouting activities is 330 cm²/hr when the crop has minimal foliage and 1400 cm²/hr when the crop has full foliage (ExpoSAC Policy 3, March 2013). Thus, the worst-case exposure scenario for scouting cabbage should be based on a transfer coefficient of 1400 cm²/hr rather than the 4200 cm²/hr used by EPA.

9.6. Level of Concern for Re-Entry Exposures

As discussed in Section 9.1 the appropriate LOC for use in the re-entry risk assessment is 4 based on an FQPA SF of 1X, and a 4X intraspecies uncertainty factor derived for male and female adults (including pregnant women). At LOC = 4, the MOE exceeds the LOC at the labeled REI for all re-entry scenarios relevant to current Dow AgroSciences labels.

9.7. Refinement of Assessment for Seed Treatments

Of the 68 exposure scenarios assessed, 36 resulted in risk estimates which were not of concern (i.e., MOEs are ≥ 100) at the level of personal protection currently required by product labels. Secondary handler (seed planter) scenarios were also evaluated and none are of concern when compared to current labels. For the remaining 32 seed treatment scenarios, MOEs were < 100 at all levels of personal protection considered and, therefore, are of potential concern.
For DAS labeled seed treatment uses, these uses exceed MOE > 100 for 69% of the seed treatment scenarios identified in the RHHRA as of potential concern. All labeled seed treatment handler uses identified in the RHHRA as of potential concern, exceed an LOC of 4 with use of gloves and therefore would not be of concern using the LOC of 4 as discussed in Section 9.2. In the case of planting previously treated seeds, gloves and respirator would be needed since there is no data for lesser PPE.

Page 173, Table H.1 Summary of Chlorpyrifos Commercial Seed Treatment Steady State Combined (Dermal and Inhalation) Exposure/Risk

Exposure scenario #9, which is listed as “Loading/applying Liquid (Micro-encaps.) for seed treatment,” appears to be mislabeled. The overall heading for this section is for wettable powders in water-soluble packaging. The name for scenario #9 should be corrected. The noted errata does not impact calculated MOEs.

9.8. PPE for Airblast Applications

Page 134, Table F.1 Chlorpyrifos Occupational Handler Non-Cancer Risk Estimates

Chlorpyrifos labels require chemical resistant headgear for overhead applications which is not taken into account in the Occupational Assessment in Appendix F. For airblast applications, chemical-resistant headgear should be included in the scenarios below:

- Single layer, gloves, PF5 respirator,
- Single layer, gloves, PF10 respirator,
- Double layer, gloves, PF5 respirator,
- Double layer, gloves, PF10 respirator.

9.9. Additional Refinement for Aerial Application

In the RHHRA, several use scenarios involving aerial application do not meet the current LOC of 100. In many of these it is the mixer/loader activity that currently fails the assessment. In discussions with the National Agricultural Aviation Association (who are submitting separate comments to the docket), several aspects of real-world practices can be incorporated to improve the Agency’s assessments.

While the Association highlights several aspects for consideration in their comments, one in particular would be expected to have a significant impact. During the growing season a typical mixer/loader will service on average two aircraft repeatedly during the day, and will be engaged for
perhaps 20 to 30 minutes at a time after which they work at other tasks until the return of the aircraft. During the day, the mixer/loaders will wash between flights; before such activities as eating or using the bathroom. So, rather than having possible chlorpyrifos residues on their skin available for absorption during the entire day, any residues would be removed from the skin by washing throughout the day.

Section 9 References


10. THERE ARE NO BYSTANDER EXPOSURE RISKS.

Summary:

- The science supports EPA’s conclusion in the RHHRA of no anticipated risks of concern from exposure to the volatilization of either chlorpyrifos or chlorpyrifos oxon from bystander inhalation exposures resulting from agricultural uses.

- DAS agrees with the Agency conclusion indicating that buffers of 0 to 25 feet are protective of both adults and children 1 to < 2 years old who may be exposed as a result of drift from treated fields. As such, buffer restrictions on product labels should be revised to reflect the conclusions of the current risk assessment.

10.1. Recent Studies Show that Volatilization of Chlorpyrifos is Not a Risk.

Page 83-84, Par. 2

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.

DAS concurs that there are no anticipated risks of concern from exposure due to the volatilization of either chlorpyrifos or chlorpyrifos oxon.

10.2. Based on the PBPK Model, Current Spray Drift Buffers Are Overly Conservative and Should Be Revised.

Page 82, Par. 2

Table 6.3.1 presents the buffer distances (feet) necessary to reach the level of concern for adults and children 1 to < 2 years old (i.e., adults, MOEs are ≥ 100; children 1 to < 2 years old, MOEs are ≥ 40) with use of certain application rates, nozzle droplet types, and application methods. The estimated buffer distances are less than those agreed to by the technical registrants in July 2012.
The Agency evaluated Adult and Children 1 to < 2 Years old spray drift buffer zones for aerial, groundboom and airblast applications and using several nozzle droplet types. Utilizing the PBPK-PD model, the Agency completed an updated assessment. DAS supports the Agency and the science based decision using PBPK, and agrees with the Agency conclusion indicating that buffers of 0 to 25 feet are protective of both adults and children 1 to < 2 years old who may be exposed as a result of drift from treated fields. As such, buffer restrictions on product labels should be revised to reflect the conclusions of the current risk assessment.

**Section 10 References**

11. DOW AGROSCIENCES CONCURS THAT THE REFINED DIETARY EXPOSURE ASSESSMENT OF CHLORPYRIFOS RESULTS IN ACUTE AND STEADY STATE FOOD-ONLY EXPOSURES THAT ARE SIGNIFICANTLY LESS THAN THE LEVEL OF CONCERN TO HUMANS.

Summary:

- DAS concurs that the refined dietary exposure assessment of chlorpyrifos results in acute and steady state food-only dietary exposures that are significantly less than the level of concern to humans.

- Considering the Acute Dietary (Food Only) Risk Assessment – Impact of 10X Intraspecies UF for Females (13-49 years old): if the 10X intraspecies uncertainty factor (UF) for adult females was reduced to 4X, consistent with other subpopulations the Agency evaluated, the aPADfood would be 11.7 µg/kg/d (aPoD/UF = 469 µg/kg/d / 40), and the food only dietary exposure of 0.15 µg/kg/d would correspond to only 1.3% aPADfood.

- Additionally, if the FQPA were maintained at 1X as proposed in the 2011 Preliminary HHRA, the dietary exposure for adult females would be reduced to <1% aPADfood.

- Considering the Steady State Dietary (Food Only) Risk Assessment – Impact of 10X Intraspecies UF for Females (13-49 years old): If the 10X intraspecies uncertainty factor (UF) for adult females were reduced to 4X, consistent with other subpopulations the Agency evaluated, the ssPADfood would be 1.95 µg/kg/d (ssPoD/UF = 78 µg/kg/d / 40), and the food only dietary exposure of 0.075 µg/kg/d would correspond to only 3.8% ssPADfood.

- Additionally, if the FQPA were maintained at 1X as proposed in the 2011 Preliminary HHRA, the dietary exposure for adult females would be reduced to <1% aPADfood.

11.1. Dietary Risk Assessment (food only) Well Below aPAD and cPAD

Page 8, Par. 5

The subgroup with the highest acute dietary (food only) exposure is females (13-49 years old) at 3.2 % aPADfood and that the subgroup with the highest steady state dietary (food only) exposure at the 99.9th percentile of exposure is children (1-2 years old) at 9.7% of the ssPADfood.

DAS concurs that the refined dietary exposure assessment of chlorpyrifos results in acute and steady state food only dietary exposures that are significantly less than the level of concern to humans.
11.2. Aggregate Risk Estimates

Page 87, Par. 1

The acute aggregate assessment includes food and drinking water only. The steady state aggregate assessment includes food, residential and drinking water exposures. Acute and steady state risk estimates for dietary (food only) exposures or for residential only (dermal, inhalation and incidental oral) exposures to chlorpyrifos are not of concern. Steady state risk estimates from food and residential exposures combined are also not of concern.

DAS concurs that acute and steady state risk estimates for dietary (food only) exposures or for residential only (dermal, inhalation and incidental oral) exposures to chlorpyrifos are not of concern. DAS also concurs that steady state risk estimates from food and residential exposures combined are not of concern.

11.3. Acute Dietary (Food Only) Risk Assessment – Impact of 10X Intraspecies UF for Females (13-49 years old)

Page 73, Par. 5

The general approach for the chlorpyrifos exposure and risk assessment can be described as follows: The PBPK-PD model was used to predict acute (24 hour) and steady state (21 day) points of departure dose levels (PoDs) which correspond to 10% RBC ChEI for the index lifestages relevant to chlorpyrifos risk assessment (children of various ages which differ due to exposure pattern, and adult females of childbearing age). The PoDs are then divided by the total uncertainty factor to determine the population adjusted dose (PAD). For food, the residue of concern is chlorpyrifos (the oxon metabolite is not an expected residue on foods). The chlorpyrifos total uncertainty factors are 100X for adult females (10X FQPA SF and 10X intraspecies extrapolation factor) and 40X for the other populations (10X FQPA SF and 4X intraspecies extrapolation factor). The chlorpyrifos exposure values resulting from dietary modeling are compared to the PAD. There are potential risks of concern when estimated dietary risk exceeds 100% of the PAD.

Page 75, Par. 2

Acute dietary (food only) risk estimates are all <100 % of the acute PAD for food (aPADfood) at the 99.9th percentile of exposure. The subgroup with the highest risk estimate was females (13-49 years old) at 3.2 % aPADfood.
As discussed in Section 7 of these comments, based on additional refinement of the PBPK model to calculate Data-Derived Extrapolation Factors, the 4X intraspecies extrapolation factor is sufficient to protect all populations including adult females. If the 10X intraspecies uncertainty factor (UF) for adult females is reduced to 4X, consistent with other subpopulations the Agency evaluated, the aPAD\textsubscript{food} would be 11.7 µg/kg/d \((aPoD/UF = 469 \ \mu g/kg/d \ / \ 40)\), and the food only dietary exposure of 0.15 µg/kg/d would correspond to only 1.3% aPAD\textsubscript{food}, as illustrated below. In the example below considering potential 10X FQPA UF and 4X Intraspecies UF, the % aPAD\textsubscript{food} is reduced by 2.5-fold.

<table>
<thead>
<tr>
<th>Population Subgroup</th>
<th>aPoD\textsubscript{food} (µg/kg/day)</th>
<th>aPAD\textsubscript{food} (µg/kg/day)</th>
<th>Food Exposure (µg/kg/day)</th>
<th>% aPAD\textsubscript{food}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults (Females 13-49 yrs)</td>
<td>469</td>
<td>11.7</td>
<td>0.150</td>
<td>1.3</td>
</tr>
</tbody>
</table>

11.4. Acute Dietary (Food Only) Risk Assessment – Impact of 10X FQPA UF for Females (13-49 years old)

Page 9, Par. 1 (EPA, 2011)

A 1x FQPA safety factor (SF) is being proposed for this preliminary assessment for acute and chronic oral exposure for chlorpyrifos since the PoDs are selected from sensitive endpoints \((RBC ChE inhibition)\) in sensitive lifestages/sexes (juveniles and/or pregnant rats).

If the FQPA SF were maintained at 1X as proposed in the 2011 Preliminary HHRA, the following impact is resultant on exposures and %aPAD\textsubscript{food}. In the example below considering potential 1X FQPA UF and 4X Intraspecies UF, the % aPAD\textsubscript{food} is reduced by 10-fold.

<table>
<thead>
<tr>
<th>Population Subgroup</th>
<th>aPoD\textsubscript{food} (µg/kg/day)</th>
<th>aPAD\textsubscript{food} (µg/kg/day)</th>
<th>Food Exposure (µg/kg/day)</th>
<th>% aPAD\textsubscript{food}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults (Females 13-49 yrs)</td>
<td>469</td>
<td>47</td>
<td>0.150</td>
<td>0.3</td>
</tr>
</tbody>
</table>
11.5. Steady State Dietary (Food Only) Risk Assessment – Impact of 10X Intraspecies UF for Females (13-49 years old)

Page 76, Par. 2

For the steady state dietary (food only) exposure analyses, children (1-2 years old) was the population subgroup with the highest risk estimate at 9.7% of the ssPADfood at the 99.9th percentile of exposure.

If the 10X intraspecies Uncertainty Factor (UF) for adult females were reduced to 4X, based on the additional PBPK modeling described in Section 8 and consistent with other subpopulations the Agency evaluated, the ssPADfood would be 1.95 µg/kg/d (ssPoD/UF = 78 µg/kg/d / 40), and the food only dietary exposure of 0.075 µg/kg/d would correspond to only 3.8% ssPADfood, as illustrated below. In the example below considering potential 10X FQPA UF and 4X Intraspecies UF, the % ssPADfood is reduced by 2.5-fold.

<table>
<thead>
<tr>
<th>Population Subgroup</th>
<th>ssPoDfood (µg/kg/day)</th>
<th>ssPADfood (µg/kg/day)</th>
<th>Food Exposure (µg/kg/day)</th>
<th>% ssPADfood</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults (Females 13-49 yrs)</td>
<td>78</td>
<td>1.95</td>
<td>0.075</td>
<td>3.8</td>
</tr>
</tbody>
</table>

11.6. Steady State Dietary (Food Only) Risk Assessment – Impact of 10X FQPA UF for Females (13-49 years old)

If the FQPA SF were maintained at 1X as proposed in the 2011 Preliminary HHRA, the following impact is resultant on exposures and % ssPADfood. In the example below considering potential 1X FQPA UF and 4X Intraspecies UF, the % ssPADfood is reduced by 10-fold.

<table>
<thead>
<tr>
<th>Population Subgroup</th>
<th>ssPoDfood (µg/kg/day)</th>
<th>ssPADfood (µg/kg/day)</th>
<th>Food Exposure (µg/kg/day)</th>
<th>% ssPADfood</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults (Females 13-49 yrs)</td>
<td>78</td>
<td>7.8</td>
<td>0.075</td>
<td>0.01</td>
</tr>
</tbody>
</table>
Section 11 References


12. DIETARY (DRINKING WATER)

Summary

- Previous DAS comments related to drinking water exposure submitted in 2011 (MRID 48636801), 2013 (MRID 49234901), and 2014 (MRID 49405101) are incorporated herein and should be considered in addition to those in this document. Many of the points are the same but are illustrated using different examples and lines of evidence. The new DAS comments on the updated 2014 EPA drinking water assessment are framed by the 2009 US EPA Guidance on the Development, Evaluation, and Application of Environmental Models, using the 21-day average concentration of chlorpyrifos as the estimated drinking water concentration (“EDWC”) needed for comparison to the DWLOC.

- EPA did not consider a toxicity study which found no hazard from chlorpyrifos-oxon levels above the maximum amounts that could occur in drinking water.

- Published watershed-scale SWAT exposure modeling provides more realistic estimates of EDWC than does SWCC with PCA=1.

- Deficiencies in the NAWQA and other monitoring program data sets do not appear to be limiting in utility to estimate EDWC for chlorpyrifos.

- The stated acceptable level of model accuracy of one order of magnitude is not associated with any written definition of regulatory objectives and therefore is questioned as being EPA policy.

- EFED analysis does not demonstrate that the model estimated concentrations reasonably compare to measured concentrations, except when realistic single-crop PCA values are used for WA crops. DAS agrees with the use of realistic single-crop PCA values as a model refinement.

- The model EDWCs cannot be characterized as providing a reasonable upper bound on the potential exposure because the magnitude of a reasonable upper bound is not defined as required by guidance (the model accuracy regulatory objective specified in US EPA, 2009).

- In view of the deficiencies of the screening-level SWCC modeling with respect to EPA guidance on accuracy required for regulatory objectives, model corroboration, and application niche uncertainty (US EPA, 2009), DAS recommends that HED rely more on the published SWAT modeling or monitoring data as representative of the true values for the chlorpyrifos EDWC in the dietary risk assessment. For those examples where EFED applied crop-specific PCA values in SWCC predictions for WA, DAS also supports the use of that refined model output as the EDWC for dietary risk assessment.
Recommended EDWC for 21-day average chlorpyrifos exposure (µg/L)

<table>
<thead>
<tr>
<th>Centile</th>
<th>MI Tart Cherries&lt;sup&gt;a&lt;/sup&gt;</th>
<th>GA Bulb Onion&lt;sup&gt;a&lt;/sup&gt;</th>
<th>CA Walnuts, Alfalfa&lt;sup&gt;b&lt;/sup&gt;</th>
<th>WA Apples, Grapes, Mint&lt;sup&gt;c&lt;/sup&gt;</th>
<th>NAWQA Agricultural&lt;sup&gt;d&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>50&lt;sup&gt;th&lt;/sup&gt;</td>
<td>4.35E-05</td>
<td>1.13E-04</td>
<td>1.15E-05/0.02</td>
<td>0.003-0.016</td>
<td>0.007</td>
</tr>
<tr>
<td>90&lt;sup&gt;th&lt;/sup&gt;</td>
<td>1.98E-03</td>
<td>1.81E-03</td>
<td>9.67E-03/0.10</td>
<td>0.009-0.040</td>
<td>&gt;0.020&lt;0.126</td>
</tr>
<tr>
<td>95&lt;sup&gt;th&lt;/sup&gt;</td>
<td>3.27E-03</td>
<td>2.79E-03</td>
<td>4.69E-02/0.18</td>
<td>0.011-0.054</td>
<td></td>
</tr>
<tr>
<td>99&lt;sup&gt;th&lt;/sup&gt;</td>
<td>7.59E-03</td>
<td>5.26E-03</td>
<td>4.21E-01/0.20</td>
<td>0.020-0.088</td>
<td></td>
</tr>
<tr>
<td>99.9&lt;sup&gt;th&lt;/sup&gt;</td>
<td>1.49E-02</td>
<td>8.70E-03</td>
<td>1.0/&gt;0.20</td>
<td>0.054-0.28</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup>SWAT (DAS Table 1).

<sup>b</sup>SWAT/MRID 44711601 (DAS Table 3).

<sup>c</sup>SWCC with crop-specific PCA, range (DAS Tables 5-7).

<sup>d</sup>Mosquin and Aldworth (2015), Table 2. The estimate for the third quartile is 0.020, and the maximum, 0.126.

12.1. Introduction

The EFED updated drinking water assessment for registration review represents a progressive development of EPA’s views on the appropriate spatial scale of exposure assessment. EPA indicates that the national screening level does not provide the most useful predictions of EDWC, because any incidence of high exposures is expected to be highly localized. Further, regional assessment does not give valuable refinements, again because exposure is not uniform within a region. EFED’s assessment is in large part focused on evaluating the characteristics of vulnerable watersheds and exploring methods to estimate chlorpyrifos surface water concentrations with improved accuracy, using a combination of refined exposure modeling and monitoring data.

Recommendations from the US EPA Guidance on the Development, Evaluation, and Application of Environmental Models (US EPA, 2009) are brought into DAS comments so that our analysis is aligned with Agency environmental modeling policy. In particular, we are interested in applying the guidance on model corroboration, or evaluation of a model’s accuracy and predictive capabilities, when comparing model results with data collected in the field. Accuracy is best characterized by considering distributions of model output and true values (US EPA, 2009).

Therefore, in the comments that follow evaluating distributions of concentration estimates, the EFED convention of comparing the 1-in-10 year predictions with the maximum observed value from
monitoring data sets is not followed. Instead, a statistically rigorous procedure was followed. Specifically, centiles from the entire distribution of values are used to enable assessment of similar points in a distribution. The 1-in-10 year SWCC prediction is generally equivalent to the $99^{th}$ to $99.9^{th}$ centile of the full distribution. Further, because HED is interested in how frequently the EDWC exceeds the DWLOC of 3.9 µg/L for an average 21-day concentration of chlorpyrifos oxon (= 4.1 µg/L chlorpyrifos), we also include the 21-day average estimates for chlorpyrifos in all of the tabular comparisons.

DAS requests that HED communicate the centile that will be used for dietary risk assessment and provide an explanation as to how it is consistent with OPP science policy. The request is made because of the novel application of a 21-day averaging period for evaluating risk of exceeding 10% AChE inhibition. Having the information will enable a more thorough analysis of SWCC model corroboration in future. In the meantime, the DAS analysis considers the following centiles: 50th, 90th, 95th, 99th, and 99.9th, assuming that the centile used for dietary risk assessment will be bracketed by this range. We also include the maximum values from the estimation methods.

In addition to model corroboration another important consideration is application niche, or the set of conditions under which the use of a model is scientifically defensible (US EPA, 2009). The related concept of application niche uncertainty, or the degree of appropriateness of a model for use under a specific set of conditions, is important for choosing among models for an application that lies outside the system for which the models were originally developed (US EPA, 2009). Application niche uncertainty is evaluated for the field-scale SWCC model and watershed-scale SWAT model (Neitsch et al. 2009) using a graphical method.

12.2. EPA Failed to Consider a Report Previously Submitted to the Agency Demonstrating No Risk from Exposure to Chlorpyrifos-oxon in Drinking Water.

As discussed previously in Section 6 of these comments, the RHHRA, the Agency makes no reference to a critical toxicological study that was submitted August 7, 2014 (Marty and Bartels (2014) (followed by Marty and Marshall (2014)). The protocol for this study was first shared with EPA in 2013, EPA provided comments on the study design in April, 2014, was notified the study was initiated in June, 2014, and results were shared in a conference call on July 17, 2014. Since oxon only forms from the degradation of chlorpyrifos during the water purification process, the highest potential exposure to oxon would be limited to the water solubility of chlorpyrifos. In this study, the biological effects from the oxon in drinking water were evaluated at a concentration based on the solubility limit for chlorpyrifos. No inhibition of RBC ChE, was found at a mean dose level of 0.098 mg/kg-bw/day. Even at this dose, which is 7X the level of oxon that could be found in water based on the solubility of chlorpyrifos, and about 88X
greater than maximum acute exposure levels in the EPA’s modeling estimates, no hazard was found. It is important to note also that RBC ChE activity has been shown to be representative and conservative of numerous other systemic tissues with respect to oxon-induced ChE inhibition. This supports the conclusion that the lack of RBC and/or brain ChE inhibition represents an absence of bioavailable oxon at these tissues.

In the assessment of potential risk from exposures from volatilization, the Agency followed the principle that no toxicity at the highest physically achievable concentration results in no anticipated risk of concern from exposure via that route. Since the study by Marty and Bartels also tested chlorpyrifos-oxon at the highest physically achievable concentration, the same principle would apply and the finding of no hazard results in no anticipated risk.

12.3. EPA Failed to Consider Previously Submitted Comments and Reports Providing Drinking Water Estimates Based on Monitoring.

In 2011 DAS submitted extensive comments to the EPA preliminary human health risk assessment for chlorpyrifos (MRID 48636801). The DAS 2011 comments remain relevant because the basic screening-level exposure assessment approach for drinking water derived from surface water used in the 2011 preliminary assessment is unchanged from the 2014 update. In the 2011 DAS comments, detailed summaries of targeted and untargeted monitoring data for chlorpyrifos and chlorpyrifos oxon were provided, indicating actual exposure was much lower than model predictions. EPA has not responded to these comments.

In 2013 a report was submitted bringing forward a new line of evidence based on NHANES biomonitoring data demonstrating modeled drinking water concentration predictions were too high (MRID 49234901). The same analysis was also submitted as part of an aggregate risk assessment in 2014 (MRID 49405101). The reliability of the EPA water concentration modeling estimates was tested by estimating chlorpyrifos exposures using urinary biomonitoring data. The Dietary Exposure Estimation Model (DEEM) was utilized to estimate exposure estimates for food and drinking water (Michigan tart cherry scenario) from EPA’s 2011 modeling estimates. For the 99.9th percentile exposure estimates, the EPA model estimates were between 16- and 52-fold higher than the biomonitoring estimates. For chronic exposures, the EPA model estimates were between 10- and 27-fold higher than the biomonitoring estimates. This shows that EPA’s modeling significantly overestimates real-world exposures. Even the EPA-estimated mean concentration estimates are higher than the 99.9th percentile concentration estimates generated from the biomonitoring data. EPA has not responded to these submissions providing the NHANES data analysis. The same analysis is also included in Reiss (2015).
DAS also points out that the 2014 submission (MRID 49405101) included summaries of monitoring data from both targeted and non-targeted studies. For the non-targeted studies statistical estimators were provided that are similar to those used in the new analysis in Mosquin and Aldworth (2015). A preliminary version of this statistical analysis actually was submitted in 2011 (MRID 48636805), supplemental to the DAS comments (MRID 48636801). Note that all estimates in all of these submissions are much lower than those from EPA screening-level modeling. EPA has not responded to the 2011 monitoring data analysis in MRID 48636805 or the 2014 data summaries in MRID 49405101.

12.4. Comments on Specific Sections of the EFED Document

Page 4, EFED Table 1. Estimated Drinking Water Concentrations Resulting from the Use of Chlorpyrifos

In the absence of well developed methods for predicting concentrations in small agricultural watersheds, EPA recommended screening-level estimates from the national screen to be used as the EDWC in dietary assessment. The following comments evaluate the utility of these estimates and suggest that watershed-scale modeling provides more reliable predictions.

DAS Table 1 reports the output from the SWCC model runs used for the summary in EFED Table 1 but reported as centiles of the entire distribution instead of the 1-in-10 year concentrations. The distributions were created by re-running the SWCC model with input files obtained from EFED and using the Excel percentile function and moving average data analysis add-in tool on the entire set of 10592 daily concentration predictions from the 30-year simulations. Also given are equivalent values from multiple year simulations of similar scenarios at the watershed scale using the SWAT model. The comparison in DAS Table 1 demonstrates the influence of the scenarios used by EFED in their screening level assessment on predicted concentrations, where conservative assumptions (including PCA=1) are incorporated and simulations are conducted with a field-scale model (SWCC). (See Reiss 2015 for a detailed description of the conservative assumptions and their influence on model predictions.) In contrast, a true watershed-scale model (SWAT) predicts more realistic lower concentrations at the collection point by simulating multiple treated fields or crops having unique application timings, accounting for actual PCA and other landscape features, and providing for routing of flow within, in this example, a third-order stream system (Williams et al. 2014). We point out that Williams et al. (2014) also reported a detailed summary of surface water monitoring data and compared equivalent points in the distributions of measured values and values predicted in the SWAT modeling that was targeted to three chlorpyrifos representative worst-case watersheds. The authors concluded the model and monitoring estimates of chlorpyrifos concentrations agreed quite well. Such was not true for preliminary
PRZM/EXAMS modeling (similar to SWCC) for the farm pond scenario. This outcome strongly suggests that the SWCC scenarios incorporating static (farm pond) and semi-static (index reservoir) water bodies and assumptions of all applications occurring on the same day to high percent cropped areas greatly overpredict actual chlorpyrifos concentrations in most real watersheds, as evidenced by the values given in DAS Table 1. All of the 21-day average SWAT predicted concentrations are much lower than the DWLOC, whereas all of the SWCC MI Tart Cherries predictions greatly exceed the DWLOC, and the SWCC GA Bulb Onion predictions are only slightly lower than the DWLOC.

Section 12 DAS Table 1. EDWC: Comparison of Model Estimated Chlorpyrifos Concentrations (µg/L), SWCC PCA=1

<table>
<thead>
<tr>
<th>Centile</th>
<th>Scenario (Daily, 21-day Average)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SWCC MI Tart Cherries</td>
</tr>
<tr>
<td>50\textsuperscript{th}</td>
<td>28.2, 28.5</td>
</tr>
<tr>
<td>90\textsuperscript{th}</td>
<td>47.2, 47.6</td>
</tr>
<tr>
<td>95\textsuperscript{th}</td>
<td>55.8, 54.5</td>
</tr>
<tr>
<td>99\textsuperscript{th}</td>
<td>82.0, 73.5</td>
</tr>
<tr>
<td>99.9\textsuperscript{th}</td>
<td>121.3, 103.0</td>
</tr>
<tr>
<td>Max</td>
<td>165.6, 112.0</td>
</tr>
</tbody>
</table>

\textsuperscript{a} From Williams et al. (2014). The only GA scenario modeled was pecans, a chlorpyrifos use pattern with greater exposure potential than bulb onion. SWAT simulations used a 96-d aerobic soil metabolism half-life. All eligible cropland in watershed assumed to be target crop and treated over a 7-d period. Daily values provided by the author.

Page 7, Par. 1

None of the monitoring programs examined to date were specifically designed to target chlorpyrifos use (except the Registrant Monitoring Program MRID 44711601); therefore, peak concentrations (and likely 21-day average concentrations) of chlorpyrifos and chlorpyrifos-oxon likely went undetected in these programs.
Although NAWQA did not specifically target chlorpyrifos, some of the sites were chosen to capture agricultural drainage (Hirsch et al. 1988) and so it seems likely that some of the NAWQA sites are at-risk for higher chlorpyrifos concentrations (Mosquin et al. 2015).

Page 7, Par. 2

In general, sampling frequency needs to be approximately equal to the duration of exposure concern. DAS disagrees with this in general, as one can still obtain useful (if biased) estimates for yearly maxima (or other quantities) with less than daily (or other frequency) sampling (Mosquin et al. 2015).

Page 8, Par. 2

Therefore, while there are many individual samples collected and analyzed for chlorpyrifos (or chlorpyrifos-oxon) across the United States, it would not be appropriate to combine these data sources to generate exposure estimates or to use these datasets to represent exposure on a national or even regional basis.

DAS suggests that the available data could be usefully exploited for this purpose. With respect to the NAWQA data, some of the sites represent agricultural land-use (indicated by a variable in the dataset), and, as noted in the EFED drinking water assessment, there are detectable levels of chlorpyrifos at many of the sites. Thus, a regression model for prediction of chlorpyrifos concentration could likely be developed for these data in a manner similar to the atrazine WARP model, which uses NAWQA monitoring locations and sampling frequencies for prediction of atrazine levels (Mosquin et al. 2015).

A further comment is that even with more limited (lower frequency) sample information, the available data can be used to place bounds on log-scale means for groups of sites (Mosquin et al. 2015). Thus, comparing the monitoring data results to the DWLOC would not be a reasonable approach for the reasons given above, including limited sample frequency, limited use information, and sampling site variability, on a national or even a regional basis.

As mentioned previously, a model similar to WARP could likely be developed for chlorpyrifos, provided suitable site locations and the technical issues addressed (Mosquin and Aldworth, 2015).

Page 8, Par. 3

In these simulations, the modeled EDWCs were within an order of magnitude of the measured concentrations. This suggests that the modeling results are not overly conservative and supports the use
of the model to estimate chlorpyrifos-oxon concentrations in drinking water.

DAS is not aware of the existence of a written statement in OPP FQPA science policy documents specifying that model accuracy within an order of magnitude is the degree of accuracy needed for human health risk assessment. EPA guidance requires this statement as a step in defining regulatory objectives (US EPA, 2009). In the absence of such a written statement, the language on Page 8 appears to be unsupported by EPA policy. Regardless, in the following detailed analysis DAS demonstrates that the EFED conclusion that modeled EDWCs were within an order of magnitude of the measured concentrations is incorrect. Under conditions of running SWCC in a screening-level tier of assessment with PCA = 1 (or other standard conservative PCA values), the modeled EDWCs are generally greater than an order of magnitude different from the measured concentrations when compared at equivalent points in the distributions of values (Jackson et al. 2005; Winchell et al., 2014). Therefore, in order to use the SWCC model output reported in EFED Table 1 for risk assessment, the written statement specifying accuracy of model predictions would need to account for this lower level of accuracy (greater than one order of magnitude) in the definition of regulatory objectives. DAS requests that OPP provide the current model accuracy regulatory objective, and if such a statement has not been adopted, recommends that OPP develop a draft regulatory objective and make it available for public and peer review. Our request comes from concern over the potential for large differences in risk conclusions resulting from order-of-magnitude model accuracy as shown in Reiss (2015).

Reiss (2015) demonstrates an order of magnitude is insufficient for reliability, as it is a difference between there being a risk and there not being a risk (his Figure 12 is duplicated below to illustrate the point).
Page 10, Table 3. Environmental Fate and Transport Characteristics of Chlorpyrifos

DAS acknowledges that EFED has developed new guidance for calculating and selecting representative half-life values from soil and aquatic transformation studies for risk assessment. However, these values are appropriate only for screening level exposure modeling purposes and represent yet another conservative factor contributing to the unrealistic SWCC model predictions. For this reason DAS advocates use of the values developed and described in Solomon et al. (2014) for higher tier exposure assessment. These are the inputs used in the SWAT model examples discussed in our comments (Williams et al. 2014).

Pages 23-28, Regional Screen

For comments on use of maximum PCA values and the assumption of applications made on the same data, see Reiss (2015). In summary, the regional screen is overly conservative as currently implemented.

Page 29, Par. 2

*We conclude from our analysis of the available surface water monitoring data that it likely underestimates chlorpyrifos and chlorpyrifos-oxon concentrations in drinking water.*
Although standard estimators underestimate they can still be useful, especially if the downwards bias can be estimated. This bias can be calculated exactly for sites with full daily time series and less precisely with less than daily sampling. However, the approach is the same as for the bias factor except that only bias is estimated (no additional protective factor) (Mosquin et al. 2015).

*These water monitoring sampling programs did not specifically target chlorpyrifos use and likely do not represent high chlorpyrifos use areas.*

It is not necessary for the monitoring programs to specifically target chlorpyrifos for the data to be useful. Provided that some (but not all) of the sites are representative of high-use areas then valuable information on chlorpyrifos concentrations at high-use sites will be available (Mosquin and Aldworth, 2015). DAS points out that chlorpyrifos remains a popular and widely used insecticide in many crops (Giesy et al. 2014), and therefore will be sampled by monitoring programs not specifically targeted to this active ingredient.

*In addition, sample timing may not have corresponded with applications or runoff events; therefore, detections cannot be directly associated with a particular use pattern or site.*

It is most important that sampling not systematically avoid periods of high runoff or use. For some of the sampling programs, the sampling was performed with high runoff periods in mind, and in other programs, without consideration of runoff (e.g., every n-day sampling). Such sampling still yields statistically useful data. We also note that sampling specifically targeted to high runoff events can lead to upwardly biased estimates of yearly quantities (e.g., weighted averages using samples collected at local maxima will overestimate 21-day averages) (Mosquin et al. 2015).

**Page 31, EFED Table 16. Surface Water Concentration Calculator Simulation Results Comparison with Orestimba Creek Surface Water Monitoring**

DAS extends the analysis conducted by EPA to provide an evaluation of the performance of various estimation approaches following Agency-wide guidance (US EPA, 2009).

DAS Table 2 presents the same information as that given in DAS Table 1 for the third scenario (Orestimba Creek) common to the EFED assessment and Williams et al. (2014) and also adds the year of daily monitoring in Orestimba Creek reported in MRID 44711601, which the author has confirmed.
represents a typical year for chlorpyrifos use and stream flow. Note that stream flow in the period when most chlorpyrifos detections are reported comes from irrigation return water and not natural base flow during the dry season in the Central Valley of California.

**Section 12 DAS Table 2.** O. Creek: Comparison of Model Estimated Chlorpyrifos Concentrations (µg/L), SWCC PCA = 1

<table>
<thead>
<tr>
<th>Centile</th>
<th>Scenario (Daily, 21-day Average)</th>
<th>MRID 44711601</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SWCC CA Almond</td>
<td>SWCC CA Alfalfa</td>
</tr>
<tr>
<td>50&lt;sup&gt;th&lt;/sup&gt;</td>
<td>1.4, 1.5</td>
<td>1.1, 1.2</td>
</tr>
<tr>
<td>90&lt;sup&gt;th&lt;/sup&gt;</td>
<td>2.8, 3.0</td>
<td>1.9, 2.1</td>
</tr>
<tr>
<td>95&lt;sup&gt;th&lt;/sup&gt;</td>
<td>3.8, 4.1</td>
<td>2.6, 3.5</td>
</tr>
<tr>
<td>99&lt;sup&gt;th&lt;/sup&gt;</td>
<td>9.0, 5.5</td>
<td>8.4, 5.0</td>
</tr>
<tr>
<td>99.9&lt;sup&gt;th&lt;/sup&gt;</td>
<td>12.5, 9.3</td>
<td>12.0, 5.4</td>
</tr>
<tr>
<td>Max</td>
<td>24.4, 11.3</td>
<td>12.4, 5.6</td>
</tr>
</tbody>
</table>

<sup>a</sup> From Williams et al. (2014). SWAT simulations used 96-d aerobic soil metabolism half-life. Chlorpyrifos applications from the California Use Reporting database; simulations run for 2000-2008. Daily values provided by the author.

<sup>b</sup> Number of values too small to calculate 99.9<sup>th</sup> centile.

Similar conclusions can be reached as those discussed in relation to DAS Table 1. The SWAT model predictions and measurement data from MRID 44711601 agree much better than do the SWCC predictions when the SWCC model is used according to EFED screening level policy (PCA = 1). All of the 21-day average SWAT predicted concentrations and the 21-day average measured concentrations from MRID 44711601 are less than the DWLOC. However, only the 50<sup>th</sup> to 95<sup>th</sup> centile SWCC predicted 21-day average concentrations do not exceed the DWLOC.

**Section 12 DAS Table 3.** presents the values in parentheses from the EFED Table 16 (output using PCA = 0.20), along with the other information from DAS Table 2. DAS Figure 1 compares the model outputs (SWCC with PCA = 1 and 0.20 and SWAT) to independent observations (MRID 44711601) as cumulative distributions.
**DAS Table 12.3.** Creek: Comparison of Model Estimated Chlorpyrifos Concentrations (µg/L), SWCC PCA = 0.20

<table>
<thead>
<tr>
<th>Centile</th>
<th>Scenario (Daily, 21-day Average)</th>
<th>SWCC CA Almond</th>
<th>SWCC CA Alfalfa</th>
<th>SWAT CA all usesa</th>
<th>MRID 44711601</th>
</tr>
</thead>
<tbody>
<tr>
<td>50th</td>
<td></td>
<td>0.3, 0.3</td>
<td>0.2, 0.2</td>
<td>0, 1.15E-05</td>
<td>0.01, 0.02</td>
</tr>
<tr>
<td>90th</td>
<td></td>
<td>0.6, 0.6</td>
<td>0.4, 0.4</td>
<td>1.22E-04, 9.67E-03</td>
<td>0.12, 0.10</td>
</tr>
<tr>
<td>95th</td>
<td></td>
<td>0.8, 0.8</td>
<td>0.5, 0.7</td>
<td>2.97E-03, 4.69E-02</td>
<td>0.25, 0.18</td>
</tr>
<tr>
<td>99th</td>
<td></td>
<td>1.8, 1.1</td>
<td>1.7, 1.0</td>
<td>2.13E-01, 4.21E-01</td>
<td>1.2, 0.20</td>
</tr>
<tr>
<td>99.9th</td>
<td></td>
<td>2.5, 1.9</td>
<td>2.4, 1.1</td>
<td>1.9, 1.0</td>
<td>&gt;1.2, &gt;0.20b</td>
</tr>
<tr>
<td>Max</td>
<td></td>
<td>4.9, 2.3</td>
<td>2.5, 1.1</td>
<td>4.5, 1.0</td>
<td>1.5, 0.21</td>
</tr>
</tbody>
</table>


b Number of values too small to calculate 99.9th centile.

**DAS Figure 12.1.** Distribution of model outputs and independent observations for Orestimba Creek 21-day average concentrations.
With the application of the PCA adjustment factor of 0.20, all of the SWCC 21-day average concentrations are lower than the DWLOC (DAS Table 10.3). DAS is pleased that EFED refined their screening level model by using the model “parameterized to reflect the actual use and the PCA” (page 31) to provide more realistic estimates of the EDWC for dietary risk assessment that agree with other lines of evidence such as watershed-scale modeling and measurement data. However, in the DAS reading of the document, EFED goes on to imply that this more realistic use of the screening level model somehow supports “the [routine] use of model EDWCs for deriving a reasonable upper bound estimation of chlorpyrifos exposure in drinking water” (p. 32) by employing the SWCC model in a manner that does not take into account this increased degree of realism. From a risk assessment perspective it is not appropriate to use an upper bound estimation (PCA = 1) when a more certain estimation is available (PCA = 0.20) that demonstrates improved model corroboration. EFED continues to support the use of conservative, early tier screening level model predictions for quantitative risk assessment that greatly overpredict EDWCs (Jackson et al. 2005; Winchell et al. 2014) with the rationale that this is the appropriate way to deal with uncertainty. In all other areas of human health risk assessment conducted in OPP, the refinement of exposure estimates in a well-defined tiered system is the norm for dealing with uncertainty in the exposure assessment and providing an appropriate level of protection. Again, DAS is pleased to see an example of such refinement done for the screening-level CA almond (walnut) and CA alfalfa model scenarios and encourages wider application of the approach in the absence of other models adopted by OPP for tiered exposure assessment.

However, on a more fundamental level of comparison, it is clear from DAS Figure 12.1 that the performance of the SWCC model is not good with respect to distribution overlap and shape in relation to the independent observations from MRID 44711601, even with a refinement in the PCA factor. The appropriate comparisons are for all crops considered in the watershed. For the EFED predictions, this requires summing the calendar day predictions for the almond and alfalfa simulations. Both SWCC output distributions are characterized by large concentrations in the upper centiles and quartiles shifted to the right. The measurement data and SWAT model predictions, in contrast, have much lower values in the upper centiles and all quartiles remain close to the y-axis (many more lower values or predictions). The superior SWAT model performance in the graphical comparison with the independent data suggests that it better fits this application niche (US EPA, 2009). Application niche uncertainty for the SWCC model appears to be greater, and it is therefore less appropriate for use under these conditions. The result is not surprising considering the difficulties of applying a field-scale model to a set of conditions related to watershed-scale processes. Moreover, the Index Reservoir scenario based on Shipman City Lake in IL does not represent conditions for the vast majority of surface water systems used as a source of drinking
water (Reiss 2015). Again, there is no reason why the SWCC model and the Index Reservoir scenario cannot be used for screening-level assessment to select cases requiring refinements in exposure predictions. It is very inappropriate to use the screening-level EDWCs for quantitative human health risk assessment. Instead, EFED should select another model for this application niche to use in higher tier exposure assessment, consistent with stated policy goals (US EPA, 2004). DAS realizes this will take some time to implement, so in the interim we suggest continued use of SWCC with more realistic inputs, starting with appropriate PCA values (as in the EFED examples for Orestimba Creek and Washington state; see also Reiss 2015).

DAS also points out that Orestimba Creek is an example of an agriculturally-dominated watershed where highly localized high exposures are expected. However, as discussed above, targeted monitoring data and refined modeling independently estimate 21-day concentrations that are less than the DWLOC.

Page 32, Par. 3

Based on this bias factor analysis, if monitoring data were available, for example, with a sample frequency of 21 days, a bias factor of 6.0 would be needed to adjust the measured concentration to obtain an upper bound estimate of the 21-day average exposure concentration. For the same sample frequency, a bias factor of 32 is needed to adjusted measured concentrations to capture an upper bound average daily concentration.

These are the largest bias factors among those calculated for each of the three Orestimba sites. If the Orestimba sites are representative of new sites on which this final bias factor would be applied, then it would be expected to typically be much more protective than the 95% level used in calculating each of the original bias factors, since the maximum observed bias factor was used as the final bias factor. Thus, the 95% protective property of the original individual site bias factors does not apply to the final bias factor – the final bias factor will tend to be far more protective, having a much higher false-positive rate (if bias factor adjusted sample values are compared to DWLOC) and smaller false-negative rate than if the true bias factors were known for site-years in question. One approach would be to set the bias factor to the amount which gives the desired level of protection over random samples of sites and of days. The resulting bias factor would still be over-protective at some sites and under-protective at others, but averaged over all sites would have the desired level of protection (Mosquin and Aldworth, 2015).
Page 33, Par. 1

In addition, the maximum detected concentrations were adjusted based on the maximum bias factor (2.99 based on a peak concentration and a sampling interval of 7 days)...”

In this analysis, model predicted peak concentrations are compared to bias-factor adjusted values, comparing predictions of one method against another. The bias-factor adjustment, however, is not a best-prediction, due to the protective requirement built into its definition. Since sample estimates for monitoring data tend to be biased downwards (Crawford 2004) we can think of the bias factor as being the product of a bias correction and a protective factor, both greater than one. For comparison of predictions, only a correction for bias need be applied (Mosquin and Aldworth 2015).

Page 34, EFED Table 19. Surface Water Concentration Calculation Simulation Comparison with Washington State Department of Ecology and Agriculture Cooperative Surface Water Monitoring Program

DAS extends the analysis conducted by EPA to provide an evaluation of the performance of various estimation approaches following Agency-wide guidance (US EPA, 2009).

EFED Table 19 presents SWCC simulations incorporating chlorpyrifos use information and PCA for the use areas represented in the WA state surface water monitoring program. The maximum detected concentration and bias factor adjusted value are also presented.

DAS Tables 12.4-6 provide the same SWCC simulation predictions expressed as centiles of the entire distribution for daily and 21-day average concentrations. Equivalent centiles of the monitoring data are also provided where applicable. We were unable to obtain the full data set for Sulphur Creek Wasteway to calculate distributions of 21-day averages. The monitoring data 21-day averages are strongly affected by the censored data/winter data substitutions (the most recent data value prior to winter, which is essentially a non-detect concentration) for lower centiles. Also, for the larger centiles, they should be somewhat biased downwards as estimates of the true values, but not by much. Moreover, little bias is expected provided that there are not meaningful concentrations in the non-sampled winter period, in which case there could be a large bias. We suppose that the monitoring program staff intentionally did not sample in the winter period assuming little use and low probability of detecting chemical residues. Note that the PCA values corrected for specific crop given in DAS Tables 12.5-6 are slightly different than those found in EFED Table 18. The DAS PCA values were calculated by taking the ratio of the concentration values presented in EFED Table 19 to account for rounding errors in the less precise
summary information. DAS Figures 12.2-4 provide the graphical comparisons of the cumulative distributions. Again, the appropriate comparison is for all crops considered in the watershed.

Section 12 DAS 4. All WA Sites: Comparison of Model Estimated Chlorpyrifos Concentrations (µg/L), SWCC PCA = 1

<table>
<thead>
<tr>
<th>Centile</th>
<th>Scenario (Daily, 21-day Average)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SWCC OR Apples</td>
</tr>
<tr>
<td>50th</td>
<td>0.17, 0.18</td>
</tr>
<tr>
<td>90th</td>
<td>0.41, 0.45</td>
</tr>
<tr>
<td>95th</td>
<td>0.60, 0.61</td>
</tr>
<tr>
<td>99th</td>
<td>1.3, 0.88</td>
</tr>
<tr>
<td>99.9th</td>
<td>2.7, 2.0</td>
</tr>
<tr>
<td>Max</td>
<td>3.8, 2.1</td>
</tr>
</tbody>
</table>

Section 12 DAS Table 5. Spring Creek: Comparison of Model Estimated Chlorpyrifos Concentrations (µg/L), SWCC PCA = 0.0384 (Apples), 0.129 (Grapes)

<table>
<thead>
<tr>
<th>Centile</th>
<th>Scenario (Daily, 21-day Average)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SWCC OR Apples</td>
</tr>
<tr>
<td>50th</td>
<td>0.007, 0.007</td>
</tr>
<tr>
<td>90th</td>
<td>0.016, 0.017</td>
</tr>
<tr>
<td>95th</td>
<td>0.023, 0.024</td>
</tr>
<tr>
<td>99th</td>
<td>0.051, 0.034</td>
</tr>
<tr>
<td>99.9th</td>
<td>0.10, 0.076</td>
</tr>
<tr>
<td>Max</td>
<td>0.15, 0.081</td>
</tr>
</tbody>
</table>
DAS Figure 12.2. Distribution of model outputs and independent observations for Spring Creek 21-day average concentrations.

Section 12 DAS Table 6. Marion Drain: Comparison of Model Estimated Chlorpyrifos Concentrations (µg/L), SWCC PCA = 0.0885 (Apples), 0.0294 (Grapes), 0.06 (Mint)

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SWCC OR Apples</td>
<td>SWCC CA Grapes</td>
</tr>
<tr>
<td>50th</td>
<td>0.015, 0.016</td>
<td>0.003, 0.003</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>90th</td>
<td>0.036, 0.040</td>
<td>0.008, 0.009</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>95th</td>
<td>0.053, 0.054</td>
<td>0.012, 0.011</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>99th</td>
<td>0.12, 0.078</td>
<td>0.023, 0.020</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>99.9th</td>
<td>0.24, 0.17</td>
<td>0.061, 0.054</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Max</td>
<td>0.34, 0.19</td>
<td>0.12, 0.063</td>
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<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
DAS Figure 12.3. Distribution of model outputs and independent observations for Marion Drain 21-day average concentrations.

Similar to the trends observed in DAS Figure 12.1, the SWCC PCA=1 estimates in DAS Figures 12.2-3. are characterized by large concentrations in the upper centiles and quartiles shifted to the right relative to the observed data. In these WA cases, however, the SWCC simulations informed by individual crop PCAs more closely agree with the observed data in both the upper centiles and all quartiles, suggesting that the simulations are more accurate than those conducted using individual crop PCAs in the Orestimba Creek watershed. For the WA sites the field-scale model with local PCA values appeared to perform adequately for use in dietary risk assessment (low application niche uncertainty).

DAS also points out that the WA watersheds are examples of agriculturally-dominated areas where highly localized high exposures are expected. However, as discussed above, targeted monitoring data and refined modeling independently estimate 21-day concentrations that are less than the DWLOC.
Page 35, Par. 2

This analysis demonstrates that the model estimated concentrations reasonably compare to measured concentrations. This suggests that if the maximum labeled rates were applied, as simulated using the SWCC, the model EDWCs provide a reasonable upper bound on the potential exposure and are not overly conservative.

The conclusion is not demonstrated qualitatively for the case where the default PCA of 1 is used in the simulation. Only when crop-specific PCA values were employed with SWCC or watershed-scale modeling was used (DAS SWAT examples) is the comparison reasonable (DAS Figures 12.1-4). Furthermore, the magnitude of a reasonable upper bound is not defined, as required by guidance (the model accuracy regulatory objective specified in US EPA, 2009). Without such a definition, it is impossible to reach such a conclusion quantitatively for SWCC predictions employing PCA = 1.

Page 35, Par. 3

These analyses and conclusions are not completely clear. For example, the text states “…these sites had samples taken less frequently than every 21 days. Thus, a larger bias factor is likely needed to account for the limited sampling at these sites in order to estimate an upper bound 21-day average concentration.” However, the bias-factor (for specified sampling design) is only precisely calculated with complete data. If the NAWQA sites have less than daily sampling, then this does not change the value of the required bias factor, it only means that it can no longer be exactly calculated and instead must now be estimated (Mosquin et al. 2015).

12.5. Conclusion and Recommended EDWC

The examples discussed in these comments incorporate approaches for improving the accuracy of estimated concentrations in drinking water from surface water sources. These include modeling vulnerable watersheds with local information on crop and use intensity. Ideally, a watershed-scale model would be used for this application niche. This will take time to develop for routine regulatory use, so in the interim field-scale modeling with local crop-specific PCA values is an appropriate practice. In addition, although targeted monitoring data is always the preferred standard for measurement data, useful estimates of concentrations can be derived from non-targeted monitoring programs, and any downward bias in these estimates can be quantified. Such bias is less important when the DWLOC is a 21-day rolling average concentration compared to shorter averaging periods.
Therefore, in view of the deficiencies of the screening-level SWCC modeling identified above with respect to EPA guidance on accuracy required for regulatory objectives, model corroboration, and application niche uncertainty (US EPA, 2009), DAS recommends that HED rely more on the published SWAT modeling or monitoring data as representative of the true values for the chlorpyrifos EDWC in the dietary risk assessment. For those examples where EFED applied crop-specific PCA values from local data in SWCC predictions for WA, DAS also supports the use of that model output as the EDWC for dietary risk assessment. However, DAS does not recommend routine use of PCAs generated by GIS analysis without confirmation by ground truthing to demonstrate accuracy.

Section 12 DAS Table 8. Recommended EDWC for 21-Day Average Chlorpyrifos Exposure (µg/L)

<table>
<thead>
<tr>
<th>Centile</th>
<th>MI Tart Cherries(^a)</th>
<th>GA Bulb Onion(^a)</th>
<th>CA Walnuts, Alfalfa(^b)</th>
<th>WA Apples, Grapes, Mint(^c)</th>
<th>NAWQA Agricultural(^d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>50(^{th})</td>
<td>4.35E-05</td>
<td>1.13E-04</td>
<td>1.15E-05/0.02</td>
<td>0.003-0.016</td>
<td>0.007</td>
</tr>
<tr>
<td>90(^{th})</td>
<td>1.98E-03</td>
<td>1.81E-03</td>
<td>9.67E-03/0.10</td>
<td>0.009-0.040</td>
<td>&gt;0.032&lt;0.12</td>
</tr>
<tr>
<td>95(^{th})</td>
<td>3.27E-03</td>
<td>2.79E-03</td>
<td>4.69E-02/0.18</td>
<td>0.011-0.054</td>
<td>6</td>
</tr>
<tr>
<td>99(^{th})</td>
<td>7.59E-03</td>
<td>5.26E-03</td>
<td>4.21E-01/0.20</td>
<td>0.020-0.088</td>
<td>0.054-0.28</td>
</tr>
<tr>
<td>99.9(^{th})</td>
<td>1.49E-02</td>
<td>8.70E-03</td>
<td>1.0/&gt;0.20</td>
<td>0.054-0.28</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\)SWAT (DAS Table 12.1).  
\(^b\)SWAT/MRID 44711601 (DAS Table 12.3).  
\(^c\)SWCC with crop-specific PCA, range (DAS Tables 12.5-7).  
\(^d\)Mosquin and Aldworth (2015), Table 2. The estimate for the third quartile is 0.032, and the maximum, 0.126.

From the above summary table, it is clear that 1 µg/L is the highest 21-day average EDWC. This maximum 99.9\(^{th}\) centile EDWC value is lower than the DWLOC calculated by EPA (3.9 µg/L for chlorpyrifos oxon or 4.1 µg/L for chlorpyrifos). Therefore, using these more realistic exposure estimates, the EDWCs are below the DWLOC, and the Aggregate (food plus water) risk assessment will pass.

Section 12. References


13. RESIDUES/TOLERANCE

13.1. Comments on Specific Sections of 2.0. HED Recommendations; 2.1 Data Deficiencies; Residue Chemistry

Page 14, Par. 1 (860.4500):
Separate magnitude of the residue studies for lemons are needed after application of Lorsban 4E and 75% WDG formulations in order to reevaluate the existing tolerance for chlorpyrifos for the citrus fruit crop group.

Regarding the requested Magnitude of Residue Study on lemon required for Lorsban-4E and Lorsban 75 WDG, DAS does not have adequate information on the study/studies with the microencapsulated formulation, which triggered this request. Prior to additional side-by-side studies, DAS requests that for transparency, the EPA make the DERs available for review by all affected registrants.

Page 14, Par. 2 (860.4500):
Magnitude of the residue studies are needed to establish a tolerance for residues of chlorpyrifos on wheat hay.

There are two DAS studies available and have been submitted for barley hay (GH-C 4132, 1995: MRID 44080401) and wheat hay (GH-C 4280, 1995: MRID 44524806). Based on wheat hay residue data (0.173, 0.140, 0.215, 0.485 mg/kg), the proposed tolerance according to the OECD calculator would be 0.9 ppm.

Page 14, Par. 3 (860.1520):
Processing studies are needed for soybean meal, hulls and refined oil.

There is one DAS processing study available on soybean (GH-C 1224, 1978). The following Tier II residue summary table shows the residue levels in processed fractions and transfer factors. Residues of chlorpyrifos in soybeans and their solvent extracted fractions were: soybeans, 0.04 ppm; hulls, 0.02 ppm; extracted meal, ND; soybean oils, 0.01-0.02 ppm; and soap stock, ND. The residues of 3,5,6-trichloro-2-pyridinol (TCP) in the same fractions were: soybeans, 0.10 ppm; hulls, 0.08 ppm; extracted meal, 0.13 ppm; soybean oils, ND; and soap stock, <0.05 ppm.

There is no need for chlorpyrifos tolerance in processed fractions since the transfer factors are <1.
<table>
<thead>
<tr>
<th>Trial ID</th>
<th>Crop Variety</th>
<th>Country Zone Location</th>
<th>Form No.</th>
<th>No. of Apples</th>
<th>Appl Rate (lb ai/acre)</th>
<th>Spray Vol (gal/acre)</th>
<th>Appl Conc (%)</th>
<th>Appl Date</th>
<th>GS at Last Appl</th>
<th>PHI (days)</th>
<th>Portion Analyzed</th>
<th>chlorpyrifos (ppm)</th>
<th>Transfer factor</th>
<th>% Recovery chlorpyrifos</th>
</tr>
</thead>
<tbody>
<tr>
<td>GH-C1224MI</td>
<td>Soybean Hark</td>
<td>United States 5A Outdoor (field)</td>
<td>M-4105</td>
<td>5</td>
<td>4</td>
<td>30</td>
<td>--</td>
<td>15-Jun-1978</td>
<td>14</td>
<td>Bean, seeds Hulls Oil, crude Oil, refined Oil, refined bleached Soapstock Solvent-extracted meal</td>
<td>0.04</td>
<td>0.02</td>
<td>0.01</td>
<td>0.02</td>
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<tr>
<td>GH-C1224N</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1</td>
<td>30</td>
<td>--</td>
<td>24-Jul-1978</td>
<td>14</td>
<td></td>
<td>0.02</td>
<td>0.01</td>
<td>0.02</td>
<td>ND</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1</td>
<td>30</td>
<td>--</td>
<td>14-Aug-1978</td>
<td>14</td>
<td>Oil, crude Oil, refined Oil, refined bleached Soapstock Solvent-extracted meal</td>
<td>0.01</td>
<td>0.02</td>
<td>0.02</td>
<td>ND</td>
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<td>2</td>
<td>30</td>
<td>--</td>
<td>05-Sep-1978</td>
<td>14</td>
<td>Oil, crude Oil, refined Oil, refined bleached Soapstock Solvent-extracted meal</td>
<td>0.05</td>
<td>0.02</td>
<td>ND</td>
<td>None</td>
</tr>
<tr>
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<td>2</td>
<td>30</td>
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<td>25-Sep-1978</td>
<td>14</td>
<td>Oil, crude Oil, refined Oil, refined bleached Soapstock Solvent-extracted meal</td>
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<td>0.02</td>
<td>ND</td>
<td>None</td>
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<td></td>
<td>0.05</td>
<td>0.02</td>
<td>0.05</td>
<td>None</td>
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</tbody>
</table>
13.2. Comments on Specific Sections of 2.1. Tolerance Considerations; 2.2.3 Recommended/Reassessed Tolerances

2.2.3 Recommended/Reassessed Tolerances
Page 15, Par. 1 (Table 2.2.3 Recommended Tolerances for Chlorpyrifos):
The following tolerances for chlorpyrifos on cotton gin by-products and aspirated grain fractions are necessary to address residues found in field trials:
Cotton, gin by-products ......15 ppm
Grain, aspirated fractions .....22 ppm
The following tolerances should be reinstated to address residues of chlorpyrifos on the milled By-products of corn and wheat:
Corn, milled by-products ......0.1 ppm
Wheat, milled by-products .....1.5 ppm

DAS accepts the recommended tolerances reassessed for Cotton gin by-products at 15 ppm and Aspirated grain fractions at 22 ppm.
DAS would also concur with the re-establishment of tolerances for Corn, milled by-products at 0.1 ppm and Wheat, milled by-products at 1.5 ppm.