Minor Crop Farmer Alliance

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February 23, 2016

Ms. Yu-Ting Guilaran, Director,
Pesticide Re-Evaluation Division
Office of Pesticide Programs
C/O OPP Docket
Environmental Protection Agency
Docket Center (EPA/DC), (28221T)
1200 Pennsylvania Avenue, NW
Washington, DC 20460-0001

Re: Pesticide Registration Review; Draft Human Health and Ecological Risk Assessments for Sulfonylureas and Certain Other Pesticides; Notice of Availability and Request for Comment, Docket ID: EPA–HQ–OPP–2015–0386 ("Notice"). Also referencing EPA-HQ-OPP-2010-0119, EPA-HQ-OPP-2008-0440, EPA-HQ- OPP-2009-0059, EPA-HQ-OPP-2008-0560, EPA-HQ-OPP-2008-0345, EPA-HQ-OPP-2008-0119, EPA-HQ-OPP-2008-0883

Dear Ms. Guilaran:

These comments are submitted by the Minor Crop Farmer Alliance ("MCFA") on the subject notice published in the Federal Register on September 25, 2015, 80 FR 57812-16. MCFA is an alliance of national and regional organizations and individuals representing growers, shippers, packers, handlers and processors of various agricultural commodities, including food, fiber, turf grass, nursery and landscape crops, and organizations involved with public health pesticides. Our members are extremely interested in the development and safe use of pest management tools including crop protection chemicals that are environmentally sound, safe for applicators and workers, and do not represent an unreasonable adverse risk to the environment, including humans.

While our commodities are often called "minor crops" or "specialty crops," they contribute to the diversity and highly nutritious diets available for the global population and to safe and aesthetic surroundings for our homes, schools, and places of business. U.S. farmers grow more than 500 types of fruit, vegetable, tree nut, flower, ornamental nursery and turf grass crops in

addition to the major bulk (row) commodity crops. Specialty crop production accounts for more than $60 billion, or approximately 40% of total U.S. crop receipts.

MCFA has reviewed the subject Notice. There are significant issues associated with the draft risk assessments. In the interests of efficiency and expediency, MCFA incorporates by reference in these comments the comments submitted by CropLife America, a copy of which are attached hereto, and the previous comments that MCFA has submitted to the docket regarding the proposed revocation of the Chlorpyrifos comments (Docket ID No. EPA-HQ-OPP-2015-0653) a copy of which is also attached.

It is clear that there are substantial infirmities associated with the procedures and policies being relied on in support the subject draft Human Health and Ecological Risk Assessments. It is strongly suggested to the Agency that it re-analyze and redo those risk assessments before moving forward. The issues involved are too significant for the Agency to proceed with the draft assessments in their current state.

Sincerely

Daniel A. Botts

Vice President Industry Resources, Florida Fruit & Vegetable Association &
Chairman, Minor Crop Farmer Alliance Technical Committee

DM_US 70454147-1.032082.0010

Minor Crop Farmer Alliance

By mail and electronically
January 5, 2016

Mr. Jack E. Housenger
Director, Office of Pesticide Programs
C/o OPP Docket
Environmental Protection Agency Docket Center (EPA/DC), (28221T)
Environmental Protection Agency
1200 Pennsylvania Ave., N.W.
Washington, DC 20460–0001

Dear Mr. Housenger:

Re: Chlorpyrifos; Tolerance Revocations; Proposed Rule; Docket ID No. EPA-HQ-OPP-2015-0653

Dear Mr. Housenger:

These comments are submitted by the Minor Crop Farmer Alliance ("MCFA") on the subject notice published in the Federal Register on November 6, 2015, 80 Fed. Reg. 69080-110.[1] MCFA is an alliance of national and regional organizations and individuals representing growers, shippers, packers, handlers and processors of various agricultural commodities, including food, fiber, turf grass, nursery and landscape crops, and organizations involved with public health pesticides. Our members are extremely interested in the development and safe use of pest management tools including crop protection chemicals that are environmentally sound, safe for

[1] Many stakeholders including members of MCFA timely filed requests for a modest extension of time to file comments on the Agency's proposed Chlorpyrifos tolerance revocation. Despite the significant impacts on stakeholders in the agricultural community if the proposed action was finalized and also the significant policy issues involved in this matter, the Agency chose to deny those requests. EPA primarily relied on the rationale that it was under a court imposed deadline to make a final decision on the Chlorpyrifos tolerances by December 30, 2016 and that the comment period for the Revised Human Health Risk Assessment (RHHRA), originally published in January 2015 (Docket No. EPA-HQ-OPP-2008-0850) and which is an essential part of the Agency's proposed tolerance revocation decision, had previously been briefly extended. Apparently the Agency believed that any modest extension of time on the tolerance revocation proposal would adversely affect its schedule and EPA was not inclined to advise the 9th Circuit that a brief extension of the comment period was needed. Although as EPA acknowledges in the subject notice it has not been able to complete its review of the comments that were received on the RHHRA, the Agency still feels compelled to proceed with the revocation proposal.

applicators and workers, and do not represent an unreasonable adverse risk to the environment, including humans.

While our commodities are often called "minor crops" or "specialty crops," they contribute to the diversity and highly nutritious diets available for the global population and to safe and aesthetic surroundings for our homes, schools, and places of business. U.S. farmers grow more than 500 types of fruit, vegetable, tree nut, flower, ornamental nursery and turf grass crops in addition to the major bulk (row) commodity crops. Specialty crop production accounts for more than $60 billion, or approximately 40% of total U.S. crop receipts.

On behalf of our members, MCFA objects to the revocation of the Chlorpyrifos tolerances (40 CFR § 180.342). Those tolerances should remain in effect. Chlorpyrifos is the only viable option in certain pest management situations and plays a very important role in the production of various crops produced by some of our members. For example, it has been the primary response to several newly emerging insect pests such as vine mealybug when it first attacked grape vines in California, as well as the brown marmorated stinkbug in other regions of the country. The revocation of the tolerances would essentially eliminate the use of the product, adversely affecting our members' interests. The affected crops include alfalfa, asparagus, beets (sugar), Cole crops, carrots, citrus, nectarine, clover, corn, cotton, cranberry, cucumber, fig, ginseng, grapes, legume vegetables (beans, peas), mint, peppermint, spearmint, onions, peanut, peppers, pineapple, apple, cherries, peach, pear, plum, prune, pumpkin, radish, rutabaga, sorghum (grain), soybeans, strawberries, sunflower, sweet potatoes, tobacco, turnip, tree nuts (almonds, hazelnut, pecans, walnuts), wheat, and triticale. [2]

The factual underpinnings, policy and scientific issues involved in this matter are significant and warrant a more complete and comprehensive investigation and review by the Agency. MCFA is extremely disappointed with the process being followed in this matter. Apparently for administrative convenience, the Agency decided to bypass the registration cancellation

[2] Growers need the current list of tolerances for these crops and for any processed fraction or food tolerance, animal feed tolerance, and animal commodity tolerance (such as, but not limited to milk, meat, or eggs) that would be associated with the use on these crops, to be maintained.

procedures contained in Section 6 of the Federal Insecticide, Fungicide and Rodenticide Act, as amended ("FIFRA") in favor of the tolerance revocation pathway offered by the Federal Food, Drug and Cosmetic Act ("FFDCA") as amended by the Food Quality Protection Act ("FQPA"), thereby avoiding the procedural safeguards established under Section 6 of FIFRA. The Agency appears to have adopted a predetermined conclusion namely that Chlorpyrifos should not be available for the agricultural community. That conclusion is after-the-fact being supported with information cobbled together from various sources, but most notably certain epidemiological papers. For example, despite EPA acknowledging that it has not completed its review of the comments on the RHHRA[3] which, in turn, involves those papers, the Agency continues to press forward with the tolerance revocation.[4] This calls into question EPA's objectiveness and transparency when reviewing the comments submitted on the RHHRA, as well as the comments being submitted challenging the Agency's proposed tolerance revocation decision.[5]

Many of MCFA's members are submitting information directly to the Agency in response to the proposed tolerance revocation. That information will include the parameters concerning their use of Chlorpyrifos and the importance to them of maintaining the current necessary tolerances.

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[3] 80 Fed. Reg. at 69083.

[4] It is understood that while EPA is relying on the epidemiological papers, the Agency has not secured or reviewed all the raw data upon which the papers are based. This is a fundamental problem. At the very least, the Agency should secure that information so it can critically evaluate the analysis and conclusions in the cited epidemiology papers, if the Agency intends to continue to rely on these papers to justify the retention of the 10X FQPA safety factor. In our view, it is unlawful for the Agency to default to the views of authors of these papers in making a regulatory decision. The Agency does not know in fact that the reported conclusions are actually consistent with the data collected for the papers. Additionally, the Agency is required to determine itself: (1) whether the participants were actually exposed to Chlorpyrifos, and if so, (2) at what dose, (3) over what time period, (4) whether the reported effects actually occurred, (5) that the measurements were accurate, and, (6) if the measurements were accurate, whether there were factors other than exposure to Chlorpyrifos which caused the purported effect. Apparently the Agency believes that the researchers' evaluation of the underlying data (assuming its veracity) must have been objective, and the Agency can default to the researchers' conclusions. Under this novel approach, adherence to Good Laboratory Practices ("GLP") and scientific merit are irrelevant for purposes of justifying a regulatory decision that will significantly adversely affect many agricultural producers.

[5] While it may prove to be a futile exercise because the Agency appears to have already made up its mind regarding the proposed tolerance revocation, MCFA incorporates by reference herein the comments submitted in Docket No. EPA-HQ-OPP-2008-0850 identifying issues with the RHHRA, including those submitted by the American Farm Bureau, Dow AgroSciences, LLC, Michigan Farm Bureau, Western Growers, CropLife America, California Citrus Quality Council, US Department of Agriculture, Northwest Horticultural Council, National Agriculture Aviation Association, California Specialty Crop Council, Western Agricultural Processors Association, California Fresh Fruit Agreement, National Cotton Council, American Mosquito Control Association, United Fresh Produce Association, California Walnut Commission, the Almond Hullers & Processors Association, Florida Department of Agriculture and Consumer Services, California Grape and Tree Fruit League, Cheminova and the Cranberry Institute.

Recognizing that providing a scientific critique of all the underlying information involved in this matter is beyond the expertise of MCFA, nevertheless there are certain issues involved that we are commenting on. These include the substantial weight that the Agency accords the epidemiological evidence to justify its proposed revocation decision. In addition, comments are provided herein on EPA's substantial reliance on screening-level drinking water models to estimate drinking water risks from potential exposures to Chlorpyrifos and EPA's expressed intention to provide the public an opportunity to comment only "to the extent practicable" on the Agency's new or modified analysis of the relevant action before it issues a final rule. *See* 80 Fed. Reg. 69083. MCFA is also concerned that the assessment approaches reflected in the Chlorpyrifos tolerance revocation proposal may serve as a precedent for the future evaluation of other pesticides. Consequently, this magnifies the importance of the issues involved, including for MCFA members that do not use Chlorpyrifos.

EPA should reconsider its reliance on the epidemiology papers in this instance

EPA should reconsider its approaches used in its revised Chlorpyrifos human health risk assessment, particularly the emphasis given to the Columbia University epidemiology paper. The information in that paper, in conjunction with two other epidemiological papers, underpins EPA's decision to increase the FQPA safety factor by an additional 10X. This additional 10X is crucial in determining whether Chlorpyrifos exceeds the total aggregate/dietary risk under FQPA. Essentially, the Agency is choosing to set aside the results of carefully conducted Chlorpyrifos laboratory animal exposure studies and instead rely on these limited epidemiological papers. Prior to this time, it was understood that the Chlorpyrifos toxicological database was very extensive and the endpoints were well understood. In this instance, however, the Agency has decided to give undue weight to the epidemiological papers, using the conclusions of those papers to redefine toxicity endpoints.[6]

[6] It is understood that there are other epidemiological publications and studies the results of which are not consistent with the conclusions of the three studies in question. Those other studies appear to indicate that at the measured levels of exposure, the evidence is insufficient to show causality between Chlorpyrifos and adverse neurological effects in infants and children. Further, a review of approximately 600 studies contracted by the EU European Food Safety Agency concluded that there is no evidence to suggest an association between pesticide exposure, including Chlorpyrifos, and neurodevelopment effects. These publications and references were identified in previous comments submitted on the RHHRA by CropLife America as referenced *supra*. MCFA respectfully requests the

MCFA agrees with those commentators who have previously advised the Agency that it is critically important that exposures referenced in epidemiological studies, including the above-mentioned three papers, be evaluated against exposures and internal doses in toxicological studies when assessing environmental exposures to a pesticide and the potential to cause harm. This is particularly important for human health conditions that can be influenced by a myriad of factors including lifestyle. When the Agency intends to override the results of carefully constructed GLP laboratory animal toxicology studies in favor of epidemiological studies, it should be assured that the exposures to the pesticide are clearly documented. Otherwise, the Agency is replacing scientific results with guesswork. By giving epidemiology studies such primacy in its decision making without having the raw data available and public consultation or discussion, EPA is reordering the hierarchy of information it uses to make regulatory decisions. This raises a host of questions that need to be considered including: What is the relationship between animal studies and human epidemiology in determining risk? Will the Agency issue guidelines for conducting epidemiology studies that will be used for regulatory decision-making? What criteria will EPA use to choose between animal studies or epidemiology studies when the results are conflicting? Based on the current record, can the Agency objectively conclude that the three epidemiological papers are rigorous enough to override the vast array of existing GLP animal toxicology studies? We think not.

As mentioned above, MCFA is concerned that EPA is making a major shift in its decision-making process in a way that will lead away from science-based decisions and to the loss of many more crop protection tools. Certainly MCFA supports efforts to protect human health and the environment. If, in its analysis, EPA determines that the science establishes that a specific use is unsafe, we will support the regulatory decision. However, the process must be scientifically reliable, robust, transparent, and objective. In this instance, basing regulatory decisions on the three epidemiology studies introduces considerable uncertainty into the regulatory process and appears to be inconsistent with sound science. Rather than advancing a

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Agency to review those 600 studies to determine whether under a weight of evidence approach continued reliance on the three epidemiological papers is appropriate.

science-based decision, the proposed tolerance revocation decision moves away from the reliable scientific data reflected in GLP animal toxicology studies.

EPA should refine its drinking water models in this instance

EPA's screening-level drinking water model is an important driver in EPA's human health risk assessment. Modeling can be a useful tool in risk assessment, but a model must be based on realistic scenarios if a credible exposure estimate is desired. Certainly, the modeling should be compared with available monitoring data to see whether or not the model is robust and reliable. At the very least, monitoring data can help refine drinking water assessments. In this case, EPA acknowledges the existence of monitoring data and suggests since the results of its modeling are within one order of magnitude of the monitoring results, the models results are not "overly conservative" and are suitable for risk assessment purposes. With all due respect, it is understood that a difference of one order of magnitude (10X) is not considered acceptable in the scientific community. What is more typical is a 3-4X difference. A difference of 10X indicates that the models' results are not reflective of the monitoring results.

The drinking water modeling used to estimate the dietary risk from Chlorpyrifos appears unrealistic because of the inaccurate assumptions used. For example, the Agency assumes that the entire watershed area is treated with Chlorpyrifos at the maximum rate on a single day, using the maximum possible amount of runoff from the treated area and that all of the runoff is drinking water. The Agency does not identify even one watershed in which all of these assumptions are true at the same time. It is understood that for Chlorpyrifos, there are almost 47,000 water data monitoring points available to the Agency that should be considered. Further, we understand that data on actual application rates and use patterns have not been used to refine modeling inputs. Rather, the models appear to rely on unrealistically exaggerated worst-case scenarios.

MCFA urges EPA to refine its drinking water modeling by using more realistic assumptions and using available monitoring data as an input in the models. The modeling is recognized as overly

conservative and does not reflect the extensive real-world monitoring data for Chlorpyrifos. EPA highlights the high level of refinement of their dietary food (residue) assessment and should require the same level of refinement for their drinking water assessments before relying on them for any regulatory decision. We believe a more refined modeling will show that there is an acceptable level of dietary risk from continued Chlorpyrifos use.

Conclusion

Chlorpyrifos is an important tool that many MCFA members rely on to control serious insect pests. Finalizing the proposed tolerance revocation will result in growers not being able to use Chlorpyrifos. In such circumstance, EPA will have unreasonably made the growers' ability to manage various pests much more difficult.[7] Reliance on unsubstantiated epidemiology papers and results from unrefined drinking water models that reflect unrealistic assumptions, is not a basis for a robust science-based decision. Before EPA finalizes its tolerance decision, the Agency should reevaluate its approach and revise it in accordance with the comments presented above. Further, the Agency should unconditionally commit to allow the public to comment on its new or modified analysis of the relevant action before it issues a final rule. The Agency's inclination to provide an opportunity for public comment only "to the extent practicable" is simply inappropriate and inconsistent with the principles reflected in the Administrative Procedure Act. The policy issues involved in this action are too significant to not allow full public comment on the analysis, including when that analysis is modified by the Agency. If the

[7] It should be noted that while EPA would be hurting our Nation's growers by eliminating the Chlorpyrifos tolerances, growers in foreign countries that use Chlorpyrifos on the commodities they export to the US should be able to continue to use the chemical, since the Agency acknowledges in the subject notice that the risk from residues in foods is acceptable. This unfair competitive advantage would not exist but for the unreasonable action that EPA is proposing.

rulemaking process requires additional time, then the Agency can so advise the 9th Circuit that the obligation to permit the interested public meaningful opportunity to comment fully on the Agency's analysis before a final decision is made necessitates an extension.

Sincerely

Daniel A. Botts

Vice President Industry Resources, Florida Fruit & Vegetable Association &
Chairman, Minor Crop Farmer Alliance Technical Committee

DM_US 69253692-2.032082.0010

[Filed via www.regulations.gov]

OPP Docket
Environmental Protection Agency Docket Center (EPA/DC), (28221T)
1200 Pennsylvania Avenue NW
Washington, DC 20460-0001

Richard Dumas
Pesticide Re-Evaluation Division (7508P)
Office of Pesticide Programs
Environmental Protection Agency
1200 Pennsylvania Avenue NW
Washington, DC 20460–0001

February 22, 2016

Re: Pesticide Registration Review; Draft Human Health and Ecological Risk Assessments for Sulfonylureas and Certain Other Pesticides; Notice of Availability and Request for Comment, 80 FR 57812; September 25, 2015; Docket ID: EPA–HQ–OPP–2015–0386 ("Notice"). Also referencing EPA-HQ-OPP-2010-0119, EPA-HQ-OPP-2008-0440, EPA-HQ-OPP-2009-0059, EPA-HQ-OPP-2008-0560, EPA-HQ-OPP-2008-0345, EPA-HQ-OPP-2008-0119, EPA-HQ-OPP-2008-0883.

Dear Mr. Dumas,

CropLife America ("CLA"), established in 1933, represents the nation's developers, manufacturers, formulators, and distributors of crop protection chemicals and plant science solutions for agriculture and pest management in the United States. Our member companies produce, sell, and distribute virtually all of the crop protection and biotechnology products used by American farmers. CLA members support a rigorous, science-based, and transparent process for government regulation of their products. CLA represents the interests of its member companies by, among other things, monitoring legislation, federal agency regulations and actions, and litigation that impacts the crop protection and pest control industries, and participating in such actions when appropriate. CLA is committed to working with the U.S Environmental Protection Agency ("EPA" or "the Agency"), as the primary federal agency responsible for the regulation of pesticides, on matters of importance to CLA member companies and the broader agricultural community.

On September 25, 2015, EPA made available for public comment its "Pesticide Registration: Draft Human Health and Ecological Risk Assessments for Sulfonylureas and Certain Other Pesticides" ("Draft Risk Assessments" or "Assessments") Docket No. EPA-HQ-OPP-2015-0386; [FR Doc. 2015-24452]. The Draft Risk Assessments identified in the Notice are intended to support the registration review of (1) a group of pesticides known as sulfonylureas ("SUs") and (2) "additional chemicals," including seven organophosphate pesticides ("OPs"). CLA previously provided comments on the Draft Risk Assessments relating to the SUs [December 24, 2015 (EPA-HQ-OPP-2015-0653-0342)] and refers the Agency to those comments, which are incorporated herein. The following comments address the Draft Risk Assessments for the seven OPs [EPA-HQ-OPP-2010-0119, EPA-HQ-OPP-2008-0440, EPA-HQ-OPP-2009-0059, EPA-HQ-OPP-2008-0560, EPA-HQ-OPP-2008-0345, EPA-HQ-OPP-2008-0119, and EPA-HQ-OPP-2008-0883]. Specific comments addressing individual OPs will be submitted by CLA members to the separate, chemical-specific dockets.

CLA appreciates the opportunity to provide comments on the Draft Risk Assessments and focuses its comments on two primary areas: (1) concerns with the transparency and openness of EPA's rulemaking process as it relates to the Draft Risk Assessments for the seven OPs; and (2) concerns related to the significant changes to EPA's risk assessment process signaled by these Draft Risk Assessments and, in particular, the September 15, 2015 document entitled "Literature Review on Neurodevelopment Effects & FQPA Safety Factor Determination for the Organophosphate Pesticides" ("Literature Review") prepared by EPA in support of the Assessments (EPA-HQ-OPP-2008-0119-0015, USEPA, 2015).

In addition to the information submitted here, CLA refers the Agency to its comments submitted on January 5, 2016, to the chlorpyrifos docket, and incorporates those comments herein. *See* CLA Comments, Chlorpyrifos; Tolerance Revocations; 80 FR 69080; November 6, 2015; Docket ID: EPA-HQ-OPP-2015-0653 ("CLA Chlorpyrifos Comments"). CLA also refers the Agency to the April 29, 2015 comments of Dow AgroSciences to Revised Human Health Risk Assessments: Chlorpyrifos Registration Review; Extension; January 14, 2015; Docket ID: EPA-HQ-OPP-2008-0850-0224 ("Dow Chlorpyrifos Comments") and the January 5, 2016 comments of Dow AgroSciences to Chlorpyrifos; Tolerance Revocations; 80 FR 69080; November 6, 2015; Docket ID: EPA-HQ-OPP-2015-0653 ("Dow Tolerance Comments").

A. Introduction

CLA's concerns arising from the September 25 Notice and Draft Risk Assessments are two-fold. The first set of concerns stems from EPA's process for disclosing the Assessments and the underlying documents on which the Agency relies. From a process perspective, EPA's exercise of its rulemaking authority has been confusing and lacked the openness and transparency with which EPA is obligated to act.

The second set of concerns stems from EPA's substantive approach to the Assessments, which continues the recent trend toward rush-to-judgment decision-making that is inconsistent with EPA's risk-based model and appears to signal a further shift away from objective assessment based on well-understood scientific methods and toward a precautionary approach that is inconsistent with EPA's statutory authority and longstanding practice.

B. CLA's Procedural Concerns Regarding EPA's Regulatory Decision-Making Process

EPA's process for making available and receiving comments on the Draft Risk Assessments for the seven OPs has been nebulous and confusing. In September 2015, EPA announced and made available the Assessments to support the registration review of the seven OPs. A key component of those Assessments is the Literature Review. Substantively, as described in further detail below, the Literature Review signals an important shift in EPA's longstanding risk assessment processes by concluding that "[t]he FQPA 10X Safety Factor will be retained for OPs for the population subgroups that include infants, children, youths, and women of childbearing age for all exposure scenarios" and "extending" the weight-of-evidence approach used with chlorpyrifos in one-size-fits-all fashion "to other OPs." Literature Review at 76, 80. *See also* CLA's January 5, 2016 Comments on Chlorpyrifos; Tolerance Revocations; 80 FR 69080; November 6, 2015; Docket ID: EPA-HQ-OPP-2015-0653.

Rather than providing open and transparent notice to the regulated community and other stakeholders, EPA buried news of this important risk assessment shift in a single sentence on page 80 of the 101-page Literature Review. The Literature Review itself is nowhere mentioned in the Notice to which these comments are directed, but is instead one of many documents buried in the numerous individual dockets for each of the OPs undergoing review.

Most remarkably, EPA has opted not to make the Literature Review itself available for separate comment. Rather, it has relied on the regulated community to comb through each docket of a multi-docket set, identify the new document, and ascertain its import, all within—initially—a thirty-day comment period—not unlike a search for a needle in a haystack. Although the existing public comment period has been extended to February 23, 2016, CLA maintains that the period remains entirely insufficient when considering the significant precedent-setting nature of this policy-setting document. *See* December 22, 2015 CLA letter (attached) to EPA (providing comment on this issue).

Indeed, the Notice triggering the comment period is entitled "Draft Human Health and Ecological Risk Assessments for Sulfonylureas and *Certain Other Pesticides*," (emphasis added), which fails to provide adequate notice to the regulated community, including CLA members, regarding which chemicals are impacted, let alone that new policy was being adopted.

In no way has this disclosure process been consistent with the openness and transparency that good government and good science require. CLA asks that EPA carefully examine its recent approach to the disclosure of its risk assessment process to ensure compliance with notice requirements and provide a transparent regulatory process that clearly and understandably identifies opportunities for meaningful stakeholder participation.

C. CLA's Substantive Concerns Regarding EPA's "Blanket" Application of the 10X FQPA Safety Factor and Reliance on Epidemiological Data.

In addition to its procedural concerns, CLA also has substantive concerns with EPA's decision to retain a 10X Food Quality Protection Act ("FQPA") Safety Factor across the OP Draft Risk Assessments and, correspondingly, EPA's novel approach to the use of epidemiological data to support this decision.

First, of significant concern to CLA members is EPA's decision to use a *blanket* 10X FQPA Safety Factor for the OP Assessments, as described in the Literature Review. This one-size-fits-all approach constitutes a fundamental change in the Agency's risk assessment process and is inconsistent with the careful evidence-based risk assessments using credible, reliable, and available data required by EPA's governing statutes. While CLA's members appreciate that EPA must carry out its statutory mandates under resource constraints and time pressures, the current high-speed, high volume approach of lumping together "categories" or "classes" of chemicals is a worrying departure from EPA's science-based, product-specific analyses and may make it difficult for EPA to adhere to its statutory authority and produce defensible regulatory decisions.

In accordance with those statutory mandates, the regulated and stakeholder communities expect EPA to make sound scientific decisions through a methodical, evidence-based, data-driven process, where haste to meet deadlines should not take precedence. The Agency should not be rushed to scientific judgement; it must take the requisite time to undertake a thorough, risk-based scientific assessment and to make the results of those assessments available to the public with sufficient time for meaningful engagement.

Second, CLA is also concerned about EPA's reliance on human epidemiological data as the support for retaining a 10X FQPA Safety Factor for the OPs. CLA notes that reliance on such data suggests a paradigm shift for EPA's risk assessment process from one that is risk- and evidence-based to one that is overly and unjustifiably precautionary, thereby contradicting the requirements, principles, and intent of the Federal Insecticide, Fungicide, and Rodenticide Act ("FIFRA") and its implementing regulations. It is of critical importance to all stakeholders that EPA's risk assessment process be based on well-understood and broadly accepted scientific concepts of risk assessment. EPA relies here on epidemiological studies of questionable validity

and relevance, while minimizing and/or excluding a robust database of toxicological and other valid and relevant data and careful, time-tested methodologies for assessing risk.

The Agency's shift toward reliance on epidemiological data is troubling for a number of reasons, not the least of which is that EPA itself has acknowledged the risks and limitations in relying on epidemiological studies for regulatory decision-making. *See* EPA's 2010 *Draft Framework for Incorporating Human Epidemiologic & Incident Data in Health Risk Assessment* at 6 ("Draft Framework") (considering how EPA will use human epidemiology and incident data in human health risk assessment and concluding that such data must be used in "the most ... transparent way"). Notwithstanding those facts, the Agency has insufficiently communicated to stakeholders how it has used, and will use, human epidemiological data now and in the future. Six years ago, in 2010, EPA submitted the Draft Framework to a FIFRA Science Advisory Panel ("SAP") for review (USEPA, 2010). The Agency has yet to finalize the Draft Framework or produce a "Response to Comments" document detailing how the Agency has addressed recommendations from either the 2010 SAP or the 2012 FIFRA SAP (USEPA, 2012), or otherwise subjected its analysis to a peer review process capable of ensuring scientific rigor and transparency. Under these circumstances, EPA's embrace of epidemiological data in the Literature Review and, correspondingly, in the seven OP draft risk assessments is premature and inappropriate.

CLA acknowledges that epidemiological investigations can potentially identify a putative association between exposure to a substance and the occurrence of disease in a population and offer estimates of the scale of risk related to a defined level of exposure or dose (Nurminen et al., 1999). However, epidemiological studies used for the evaluation or setting of guidelines must adhere to the same quality and transparency requirements as other data submitted to and relied on by the Agency. We are highly concerned that the epidemiological data selected in the Literature Review possibly have not adhered to the same quality and transparency requirements as is required, by law, for other data submitted to and relied on by the Agency.

Third, in opting to rely on the epidemiological data, EPA has essentially cast aside the extensive, robust database of toxicity studies on OPs conducted according to scientifically validated test methods reviewed and accepted by the Agency.

Current EPA regulation of OPs based on cholinesterase ("AChE") inhibition remains adequately protective of human health. The weight of evidence ("WoE") from the existing toxicity database supports a highly conservative regulatory point of departure based on replicated Good Laboratory Practice ("GLP") studies in multiple species, durations and routes of administration. Outcomes from these animal studies are further corroborated by standard, long-used physicochemical and mechanistic principles. EPA's WoE conclusions and proposed actions based on the recent Literature Review are inconsistent with a vast number of available

and peer-reviewed scientific studies. The extant human epidemiological data do not support a low dose effect, or a more conservative endpoint for regulation. Uncertainty created by consideration of epidemiological data, subsequent to review of primary data, is not aligned with appropriate risk-based scientific study practices and therefore should not dictate retention of the 10X FQPA Safety Factor across the class of compounds.

Fourth, CLA has significant concerns regarding the specific epidemiological studies on which EPA is basing its regulatory decision. The Literature Review is based on three major U.S.- based prospective birth cohort studies: (1) Mothers and Newborn Study of North Manhattan and South Bronx conducted by Columbia University, or the "Columbia Study/Cohort;"[1] (2) Mount Sinai Inner-City Toxicants, Child Growth and Development Study, or the "Mount Sinai Study/Cohort;"[2] and (3) Center for Health Assessment of Mothers and Children of Salinas Valley (CHAMACOS) conducted by the University of California Berkeley, or "CHAMACOS Study/Cohort"[3] ("the Studies"). CLA understands that the underlying data for those Studies have never been disclosed to the Agency, preventing any opportunity—by the Agency, the scientific community, or otherwise—to verify or replicate the Studies or test their connection (if any) to causation. Moreover, EPA's reliance the Studies whose raw data are unavailable ignores EPA's own standards imposed on registrants, *e.g.*, the robust data quality assurance required by federal (40 CFR Part 160) and EPA data quality guidelines, particularly given that the Studies were federally-funded. *See* CLA Chlorpyrifos Comments at 3; Dow Chlorpyrifos Comments at 11, 39-40; Dow Tolerance Comments at 16-17.

Of further concern is that EPA's review of the relevant epidemiological literature is incomplete and excludes discussion of recent publications that show no adverse associations with OPs and neurodevelopment (Cartier et al. 2015; Engel et al. 2015; Yolton et al. 2013). The exclusion of negative studies, compounded by inherent publication bias, shifts the weight of evidence in favor of inappropriately inflating the interpretation of suggested associations between OP exposure and neurodevelopmental effects.

The following further points also should be considered in relation to the Agency's use of sound science in risk-based regulatory decision-making:

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[1] Perera FP, Illman SM, Kinney PL, Whyatt RM, Kelvin EA, Shepard P, Evans D, Fullilove M, Ford J, Miller R, Meyer I, Rauh V, 2002. "The challenge of preventing environmentally related disease in young children: community-based research in New York City." *Environ Health Perspect* 110, 197–204

[2] Berkowitz GS, Obel J, Deych E, Lapinski R, Godbold J, Liu Z, Landrigan PJ, Wolff MS, 2003. "Exposure to indoor pesticides during pregnancy in a multiethnic, urban cohort." *Environ Health Perspect*; 111, 79-84.

[3] Eskenazi B, Harley K, Bradman A, Weltzien E, Jewell NP , Barr DB, Furlong CE, Holland NT, 2004. "Association of in utero organophosphate pesticide exposure and fetal growth and length of gestation in an agricultural population. *Environ Health Perspect*." 112, 1116 – 24.

- There are open questions regarding linkage between exposure to pesticide products or their uses and the reported health outcomes reported from the epidemiological studies relied on by EPA.
- EPA has failed to provide benchmarks for exposure measurements, or discernments or scientifically appropriate and predictive mixes of dialkylphosphates ("DAPs") that correspond to exposure to specific species and all families of OPs.
- The robust and complete animal and human database of GLP toxicology studies does not support the conclusions drawn from the epidemiological data (see Appendix A).
- The lack of access to raw data is especially problematic with exposure analyses in the EPA-selected epidemiological studies. For both scientific and regulatory validity, these types of underlying raw data are indispensable.
- The Agency has seemingly hand-picked studies, relied upon "suggestive evidence" and ignored statistical data in an effort to support their overall conclusions from the selected epidemiological data.
- When the conclusions based on epidemiological data and toxicity data lack alignment; merely adding an uncertainty factor is inappropriate. For EPA to establish causation and make final conclusions about risk and any resulting regulatory decision, the Agency must evaluate the combined weight of evidence.

CLA directs the Agency to Appendices A-C of this document for additional information related to EPA's reliance on epidemiological data, interpretation of causal relationships and of mechanistic data, and the Agency's implementation of the 10X FQPA Safety Factor.

D. CLA's Requested Path Forward

CLA firmly believes that there are serious procedural and scientific issues with the Agency's proposal to retain the 10X FQPA Safety Factor for all OPs based on the Literature Review. The Agency should not rush to make a regulatory decision that will set a flawed precedent for all future risk assessments for OPs and for other classes of pesticide products. Agency decision-making must adhere to scientific peer review and public participatory processes and carefully consider input from public stakeholders. To that end, CLA specifically requests that EPA:

- Halt any regulatory action on the OPs based on the retention of a 10X FQPA Safety Factor until the Agency has (1) reviewed and responded to all SAP and other comments and recommendations related to the Draft Framework document and (2) revised and reissued the Draft Framework for public comment, alongside a "Response to Comments" document;
- Hold itself to the same data quality standards imposed on registrants, including access to the raw data from the Studies, ensure that the Agency has the scientific expertise and capacity to review the raw data, perform all appropriate analyses on that raw data with

particular focus on the exposure assessment, and control confounding and effect modifiers (e.g., lead), and evaluate consistency across studies; and

- Withhold regulatory action on this class of chemicals until it has confirmed exposure to OPs (pre- and postnatal) and any link between any exposure and the reported neurodevelopmental effects at the individual level.

* * *

EPA and its stakeholders benefit from a careful, comprehensive administrative process and regulatory decision-making based on complete, careful, science-based risk assessment. CLA appreciates your attention to these comments in response to the Notice and referenced dockets and looks forward to continued work with you on these matters.

Sincerely,

Tamika D. Sims, Ph.D.
Director, Human Health Policy
CropLife America

Cc: Mr. Jack Housenger, Director, Office of Pesticide Programs, USEPA
Mr. Rick Keigwin, Deputy Office Director for Programs, USEPA
Dr. Thomas Burke, Deputy Assistant Administrator, Office of Research and Development, Science Advisor, USEPA

Attachments: CLA letter to EPA Regarding OP Comment Period, December 22, 2015

Appendix A- Use and Application of Epidemiological Data

1. The EPA Framework document was designed in accordance with recommendations of the Advisory committee and Scientific Advisory Panel (SAP), whose input has been repeatedly sought by the Agency in an effort to ensure objectivity and transparency in its pesticide risk assessment process. To evaluate the literature on neurodevelopment effects and OP exposure, the EPA must first follow its own Draft Framework and appropriately evaluate both the epidemiological and toxicological evidence. The 2010 Draft Framework describes using a modified Bradford Hill criteria to evaluate the weight of evidence of epidemiological and toxicological data. In the Literature Review, EPA has not fully considered these criteria, recommended in its own 2010 Draft Framework, and makes statements that are unsubstantiated by the reviewed publications. The Bradford Hill criteria include (Hill, 1965):

   - strength and consistency of the association
   - the temporal relationship of the association
   - the biological gradient (dose response curve)
   - the biological plausibility of the association given the information on disease etiology
   - the specificity of the association

2. The Studies[4] cited in the Literature Review were not designed to evaluate the association between OP exposure and neurodevelopmental outcomes for use in risk assessments (Perera et al.2002; Berkowitz et al. 2003; Eskenazi et al. 2004). Human epidemiological data lack dose response concordance and are limited by insufficient exposure assessments. Human epidemiology should not and cannot be used to establish a causal relationship between OP exposure and neurodevelopmental outcomes based on significant limitations of the exposure assessment, control of confounding factors and effect modifiers.

   Also of note, authors of the Columbia University study fully admit that their epidemiological study was not designed to evaluate temporal concordance and if a

[4] Throughout these appendices, "Studies" refers three major U.S based prospective birth cohort studies: (1) Mothers and Newborn Study of North Manhattan and South Bronx conducted by Columbia University, or the "Columbia Study/Cohort;" 2) Mount Sinai Inner-City Toxicants, Child Growth and Development Study, or the "Mount Sinai Study/Cohort;" and 3) Center for Health Assessment of Mothers and Children of Salinas Valley (CHAMACOS) conducted by the University of California Berkeley, or "CHAMACOS Study/Cohort." "Literature Review" refers to EPA's 2015 Literature Review on Neurodevelopment Effects and FQPA Safety Factor Determination for the OPs.

relationship seems to exist, it may be due to chance. The Agency has, in this case, over extended the interpretation of the Studies' ability to discern temporal concordance despite the strong clarifications provided by the study authors. For instance, highlighting the dramatic differences in measured chlorpyrifos levels pre-cancellation and post cancellation of residential uses, as attempted by the Agency, is not logical simply due to the Studies' design.

Several other researchers have also reviewed this same set of human epidemiological data used in the Literature Review and reported equivocal evidence of adverse human health effects associated with exposure levels below acetylcholinesterase inhibition. (Burns et al. 2013; Eaton et al. 2008; Li et al. 2012; Prueitt et al. 2011; Reiss et al. 2015). In their review of OPs, Reiss et al. (2015) summarized that "the available evidence does not establish that low-level exposure to OP insecticides causes adverse birth outcomes or neurodevelopmental problems in humans."

For additional in-depth comparison of approaches to using the epidemiological data Table 1 (below) compares the guidance language found in the 2010 EPA Draft Framework with the epidemiology review of EPA, Burns et al. and Reiss et al.

Table 1: Comparison of statements directly taken from the EPA Draft Framework (EPA, 2010) to EPA Literature Review (EPA, 2015) and two peer-reviewed Review studies (Reiss et al. 2015; Burns et al. 2013).

EPA Literature Review statements	Reiss et al., 2015 statements	Burns, et al., 2013 statements
Framework: Dose-response relationships are identified for each key event; such data can be presented in figures or tables for ease of evaluation. Dose-response relationships are compared among key events. Temporal data can be presented in figures or tables for each evaluation. In this part of the analysis, data are evaluated to ensure that the temporal sequence of events is supported.		
Dose response and temporal concordance: actual level of such exposure during the critical window(s) of susceptibility is not known. With respect to the timing of exposure, across the epidemiology database of studies, the maternal urine, cord blood and other (meconium) measures provide evidence that exposure did occur to the fetus	It is scientifically invalid to test numerous associations and choose the statistically significant ones as being the etiologically correct ones while dismissing the statistically non-significant associations. Temporality...perinatal or early childhood exposures could plausibly be related to subsequent neurodevelopment....However, because little is known about the timing of various neurodevelopmental	Dose response: Few of the epidemiological data were reported in this context. Many of the cohorts reported linear regression coefficients for urine or blood levels...but log-transformed data hindered direct interpretation of coefficients.... The CHAMACOS study did stratify exposure by three urinary levels (< detection, < median, ≥ median)

during gestation, but the actual level of such exposure during the critical window(s) of susceptibility is not known. While uncertainty exists as to actual OP exposure at (unknown) critical windows of exposure, EPA believes it is unlikely individuals in the epidemiology studies experienced RBC AChE inhibition.	impairments, it is unclear whether environmental exposures in early gestation, late gestation, infancy, early childhood, or later childhood – or perhaps a combination of these – are most etiologically relevant....	for TCPy and MDA (Eskenazi et al., 2004).
Framework: Strength, consistency, and specificity of association of key events and the toxic effect. Complete assessment and presentation of the relationships among key events, precursor lesions, and the toxic effect is provided. In this analysis, the consistency of observations across studies of different designs is described. EPA Office of Pesticide Programs (OPP) will place higher confidence in results that are replicated or reproduced from multiple studies. When animal and epidemiological 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.		
Strength, consistency and specificity: Among the epidemiological studies, two of the cohorts (CCCEH and ELEMENT) have focused on chlorpyrifos whereas the other studies (Mt. Sinai cohort, CHAMACOS cohort, CHARGE study, Bouchard et al., 2011)[5] have focused on less specific biomarkers (i.e., DAPs) and are not specific to any particular OP. When considered in concert, the epidemiological studies provide consistent findings for some outcomes.	Strong versus weak associations also are not objectively defined, especially for continuous exposures and outcomes....These associations with large ORs merit a closer look. Most of these and other reported associations are statistically non-significant, making them consistent with no association between OP metabolites and neurodevelopmental outcomes.	The "strength" of association is a term for the magnitude of a relative risk (RR) estimate (e.g., odds ratio, risk ratio, or rate ratio). The strength (magnitude) of a regression coefficient is less straightforward since the estimate is reflective of statistical transformation and the unit of measure (e.g., inches or centimeters).
The CHAMACOS and Mt. Sinai cohorts that measured neurological effects at birth (the Brazelton index), reported a	In four studies conducted in four different settings, neonatal behavior was evaluated using the Brazelton	Urinary DAP levels were considered to reflect exposure to OP as a class. The epidemiological literature was

[5] Prospective birth cohort studies (1) Mother's and Newborn Study of North Manhattan and South Bronx conducted by Columbia University, or the "CCCEH" "Columbia Study/Cohort;" Mount Sinai Inner-City Toxicants, Child Growth and Development Study, or the "Mount Sinai Study/Cohort;" Center for Health Assessment of Mothers and Children of Salinas Valley (CHAMACOS) conducted by the University of California Berkeley, or "CHAMACOS Study/Cohort," Childhood Autism Risks from Genetics and the Environment or "CHARGE" study, California, Child Cohort, Early Life Exposures in Mexico to Environmental Toxicants or "ELEMENT" study.

putative association with OPs (Engel et al., 2007; Young et al., 2005).	Neonatal Behavioral Assessment Scale, the NICU Network Neurobehavioral Scale, and the Neonatal Behavioral Neurological Assessment (Engel et al. 2007, Yolton et al. 2013, Young et al. 2005, Zhang et al. 2014). Three of these four studies found an association between prenatal OP metabolite levels and poorer reflexes at or shortly after birth (Engel et al. 2007, Young et al. 2005, and Zhang et al. 2014). Three studies also showed no association with any other adverse neonatal behavioral outcomes (Engel et al. 2007, Yolton et al. 2013, and Young et al. 2005). The statistically null results for poorer reflexes in the HOME[6] study (Yolton et al. 2013), in which newborns were older at the time of assessment than those in the other three studies, may suggest that the association is no longer detectable by age 5 weeks.	limited to the CHAMACOS and Mt. Sinai birth cohort studies. Thus, consistency of results in both studies was evaluated. The number of abnormal reflexes in newborns was the only health outcome statistically associated with maternal DAP levels in both studies (Young et al., 2005; Engel et al., 2007). The specific pesticides contributing to urinary DAP levels may be different for the California farm worker participants (CHAMACOS) and the urban New York City participants (Mt. Sinai Study).
...the three US cohorts each reported evidence of impaired mental and psychomotor development.	Although all three studies that measured pre- or perinatal OP metabolites and used the Bayley Scales of Infant Development found a significant inverse association between OP metabolite levels and scores on the Mental Development Index (Engel et al. 2011, Eskenazi et al. 2007, Rauh et al. 2006), this apparent consistency is no longer evident after a closer examination of results.... Thus, none of these studies detected persistent decrements in the Mental Development Index related to OP insecticide exposure across infancy and early childhood age groups.	In summary, adverse associations were reported for maternal DAP and BSID: MDI assessed at 24 mo in the CHAMACOS study, and for maternal DAP and BSID: MDI assessed at 12 mo among Black/Hispanic participants in the Mt. Sinai study.... The divergent findings for BSID by maternal and child urinary levels in the CHAMACOS study and the racial differences in the Mt. Sinai study indicate poor internal consistency for OP insecticides, in general, with these scores.

[6] A Cincinnati Cohort examining Health Outcomes & Measures of the Environment, or "HOME" study

	No adverse cross sectional associations between child urinary OP metabolite levels and mental development at 24 months were reported in CHAMACOS (Eskenazi et al. 2007) and the Shanghai study (Guodong et al. 2012), and most (three out of four) studies did not detect any significant associations with infant psychomotor development (Engel et al. 2011, Eskenazi et al. 2007, Guodong et al. 2012).	The lack of consistent analyses across studies by age of testing and racial disparity further clouds the etiologic role of OP as a class and BSID scores.
Attentional problems and ADHD were reported by CCCEH, Mt. Sinai, CHAMACOS, and ELEMENT investigators with additional support from Bouchard et al. (2010). Several studies have now documented suggestive or positive associations between OP exposure and autism spectrum disorders (Rauh et al., 2006; Shelton et al., 2014; Furlong et al., 2014; Eskenazi et al., 2007; Eskenazi et al., 2010).	Six studies in five settings evaluated ADHD and other attention problems in preschool- and school-aged children...Significant positive associations between prenatal or child OP metabolite levels and some measures of ADHD or attention problems were detected in the CCCEH study at age 36 months (Rauh et al., 2006), in the CHAMACOS cohort at age 5 years (Marks et al., 2010), and in NHANES at ages 8 - 15 years (Bouchard et al., 2010), but not in the CHAMACOS cohort.... The consistency of results across studies is difficult to judge, due to differences in measurement instruments, analytic approaches, the timing of metabolite measurement, and the timing of neurodevelopmental assessment; the internal inconsistency of the findings in the CHAMACOS cohort also complicate interpretation. Overall, the findings for ADHD and attention problems were approximately equally balanced between positive and null. Other behavioral problems in preschool- and school-aged children were measured in three study settings using the Child Behavior Checklist and the Strengths and Difficulties Questionnaire (Eskenazi et al. 2010, Eskenazi et al. 2007, Oulhote and Bouchard 2013, Rauh et al. 2006). The	Despite the many analytical comparisons reported ... the number of comparisons that evaluated the same pesticide (or its metabolite) and the same health endpoint was small. A number of statistically significant observations have not been "tested" in the available published literature thereby limiting the ability to determine consistency across independent studies.....CPF levels were strongly associated with CBCL-assessed ADHD problems in the CCCEH study (OR = 6.50, 95% CI 1.09–38.69) (Rauh et al., 2006), but not for TCPy levels in the CHAMACOS study (OR = 0.59, 95% CI 0.21–1.68) (Eskenazi et al., 2007). ADHD was not evaluated by the Mt. Sinai study.

	only specific behavioral outcome measured in more than one study was pervasive developmental disorder based on the Child Behavior Checklist, which was positively associated with pre- or perinatal OP metabolite levels in the CCCEH study (Rauh et al. 2006) and the CHAMACOS Study (Eskenazi et al. 2007).... It is unclear whether the global total difficulties scale – which was not significantly associated with child urinary DAP, DMP, or DEP metabolite levels in the Canadian Health Measures Survey (Oulhote and Bouchard 2013) – is comparable to that for pervasive developmental disorder based on the Child Behavior Checklist. (NOTE Furlong et al., 2014 and Shelton et al., 2014 were not reviewed by Reiss et al., 2015).	
Finally, each of the three US children's cohort study authors observed an inverse relation between the respective prenatal measures of chlorpyrifos and intelligence measures at age 7 years.	Four studies in four separate settings assessed cognitive outcomes in preschool- and school-aged children....Two studies found an inverse association between prenatal OP metabolite levels and the Wechsler Working Memory Index at 7 years (Bouchard et al., 2011, Rauh et al., 2011), but one study did not (Engel et al., 2011), and another found no association based on child DAP levels (Lizardi et al., 2008).... Three of four studies detected no significant associations between prenatal or child OP metabolite levels and the Wechsler Full-Scale IQ, Processing Speed, and Verbal Comprehension Scales (Engel et al., 2011, Lizardi et al., 2008, Rauh et al., 2011).	In the CHAMACOS Study, two DAP collections averaged over pregnancy were associated significantly and inversely with all WISC-IV measures reported. The DAP levels collected in the first half of pregnancy were only associated with Verbal Comprehension, whereas DAP levels collected in the second half of pregnancy were only associated with the Full Scale IQ. Child DAP levels were not associated consistently with WISC-IV performance. In the Mt. Sinai Study, participants were evaluated for intelligence testing between ages 6 and 9 yr. (Engel et al., 2011). Results were reported separately for the two Wechsler tests and for the combined population (ages 6–9

		yr). Regardless, none of the associations of DAP with WPPSI or WISC outcomes or the outcomes for the combined populations was statistically significant.
The most commonly reported outcome was cognitive dysfunction, and although it was overall consistent there were again differences in **cognitive specificity**, gender differences, or dose response. Quite a few studies also report changes in motor activity and sensory function in offspring, but there generally fewer studies that assess social interactions for OPs other than chlorpyrifos.	In summary, multiple studies reported a variety of associations of OP metabolites....When studies were closely compared according to design, exposure metric, timing of exposure measurement, age group of subjects, and neurodevelopmental test, at most only two studies were directly comparable....Thus, using our *a priori* requirement of three independent studies to evaluate the weight of epidemiological evidence, the available data are insufficient to establish consistent associations between specific OP metabolites and specific neurodevelopmental outcomes. No specificity is evident in the relationships between any particular OP insecticide and any particular neurodevelopmental outcome.	
Framework: Biological plausibility and coherence -- Determination of whether key events and the sequence of events are consistent with current biological thinking, regarding both the specific toxic effect in general and the specific chemical under review. Specific to epidemiology and human incident data, the degree to which reported outcomes compare with those expected from a known MOA and/or with health outcomes for other chemicals in the same chemical class are discussed.		
Biological Plausibility and coherence; The Cancer Guidelines further state that *"lack of mechanistic data, however, is not a reason to reject causality."* Despite all these uncertainties and differences in study design, multiple investigators have identified associations with neurodevelopmental outcomes such as ADHD/behavioral problems and autism spectrum, in relation to OP exposure. There	There are no known biological pathways for OP insecticides to cause the neurodevelopmental effects examined in the epidemiological studies. Although the lack of established pathways does not mean that they do not exist, the existing evidence does not support a causal interpretation. No apparent interactions or patterns suggesting higher susceptibility with lower PON1 activity were detected. Altogether, these limited findings do not provide consistent, coherent evidence to support the hypothesis that	At best, the DAP metabolites provide a general range of overall access to OP pesticides. The biological plausibility for a causal effect of OP exposure on neurobehavioral outcomes collectively is not well-supported by the recent animal literature. The animal data at lower dose ranges tested suggest that effects on neurobehavioral outcomes of different OP, such as diazinon, parathion, and CPF are not

is evidence of delays in mental development in infants (24-36 months), attention problems and autism spectrum disorder in early childhood, and intelligence decrements in school age children who were exposed to OPs during gestation	low PON1 activity levels augment individual susceptibility to impaired neurodevelopment from OP insecticide exposure	consistent as described earlier in the Animals section. In fact, the authors of the only studies that allow comparison of three OP on similar serotonergic, molecular, cognitive, motor, and emotional outcomes conclude that the neurobehavioral and neuropharmacologic data suggested that OP exerted disparate effects of noncholinergic modes of action on the developing nervous system. (Mink et al., 2012; McKone et al., 2007; Lowe et al., 2009; Eaton et al., 2008) Other studies demonstrating a more consistent dose-response effect on cholinergic systems provide more compelling evidence of a potential common mode of action based on downstream effects of AChE inhibition. However, these effects occur at dose levels that also produce AChE inhibition.

3. EPA does not explain or justify the exclusion of 57 publications on exposure and 16 publications on methods and exposure validation identified in the literature search. Including this data would better inform the validity of the risk estimates in the Studies.

4. In addition to the epidemiological Studies lacking sufficient exposure assessments, they are not able to adequately control for confounding and other effect modifying factors. Study authors have concluded that while certain confounding factors were evaluated, there has not been a complete evaluation of all confounding factors and effect modifiers. Prenatal and postnatal lead exposure, for example, is an important factor to consider with regards to neurodevelopmental effects and lower intelligence quotient measures in lower income populations. In 2012, CDC announced that there is no threshold of safety for lead exposure and subsequent neurodevelopmental health outcomes (http://www.cdc.gov/mmwr/preview/mmwrhtml/su6104a1.htm). Until the

raw data from the Studies have been independently reviewed by the Agency, it remains unclear whether the neurodevelopmental health effects are due to OP exposures or other factors.

5. EPA fails to appropriately "weigh" both the epidemiology and toxicology evidence as the EPA 2010 Draft Framework advises. Additionally, the weight of epidemiological evidence from the Studies lacks consistency; findings are not replicated across various subpopulations of potential OP exposure. There is no detailed discussion about how the Agency determines that some outcomes are sufficient with respect to strength, consistency and specificity. Study findings are inconsistent; for example, in regards to the Attention Deficit Hyperactivity Disorder (ADHD) outcome, the EPA provided only an incomplete assessment of the consistency across studies of key events. Reiss et al. (2015) concluded that the "findings for ADHD and attention problems were approximately equally balanced between positive and null" for the Studies.

   The Agency has not conducted nor properly documented a full systematic review of the literature in an unbiased manner. Until this comprehensive systematic review is completed and peer reviewed by a scientific panel with public stakeholder involvement, no regulatory action should be initiated.

Appendix B- Mechanism of Action, Causal Relationships

1. Extensive animal data for the organophosphates (OPs) demonstrate a clear dose response relationship with the regulatory point of departure established on an early precursor event. Based on the current empirical evidence that is focused on only OP exposures, the weight of evidence supports a 10% inhibition of acetylcholinesterase (AChE) as the most conservative point of departure for OP risk assessments; the early key event of inhibition of acetylcholinesterase has been established to be overly conservative in the protection of subsequent neurodevelopmental health effects.

2. In the absence of discriminatory analyses, urinary dialkylphosphate (DAP) metabolites are not biologically adequate predictors of exposure to any specific pesticide. Without confirmed OP exposure (which can only come from a stoichiometrically consistent mixture of DAPs, in combination with the unique elemental properties of phosphorus) additional regulatory action is unwarranted.

3. The Agency did not fully consider the strength and consistency between animal toxicity and mechanistic data and their concordance with standard physical organic attributes of this class of compounds. Organophosphorus insecticides represent one of the few unique compound classes where the underlying biochemical lesion (nucleophilic attack of electropositive phosphorus on AChE's serine hydroxyl group) coincide with established physical organic chemistry principles (simple alkaline hydrolysis) and are also in concordance with pharmacodynamic outputs from animal toxicology studies.

   Further, the fact that the Studies[7] fail to identify the unique and scientifically predictive DAP fingerprints that are specific to OP exposure is a significant methodological deficiency the Agency should acknowledge in its Literature Review.

   The Studies are also not suitable to address the underlying Structure Activity Relationships (SARs) on OPs, whose chemical structural properties are integral to EPA's risk assessment conclusions. Accordingly, the biological coherence demonstrated across

[7] Throughout these appendices, "Studies" refers three major U.S based prospective birth cohort studies: (1) Mothers and Newborn Study of North Manhattan and South Bronx conducted by Columbia University, or the "Columbia Study/Cohort;" 2) Mount Sinai Inner-City Toxicants, Child Growth and Development Study, or the "Mount Sinai Study/Cohort;" and 3) Center for Health Assessment of Mothers and Children of Salinas Valley (CHAMACOS) conducted by the University of California Berkeley, or "CHAMACOS Study/Cohort." "Literature Review" refers to EPA's 2015 Literature Review on Neurodevelopment Effects and FQPA Safety Factor Determination for the OPs.

this structure activity domain far exceeds the empirical nature of conclusions from even well designed epidemiological studies.

Appendix B, Table 2, summarizes OP-specific metrics associated with the SAR-based limitations of the Studies evaluated by the Agency.

Table 2. List of EPA Literature Review (EPA, 2015) Organophosphorus Insecticides and Some Basic SAR related Properties:

Chemical	PC Code	CAS No.	Bioactive Forms	Aging Potential	Physico-Chemical Properties
Dicrotophos	035201	141-66-2	1: P=O	Highly reactivatable	Log P: 0.3; Miscible
Fosthiazate	129022	98886-44-3	4: P=O, P=S, N-P-S; N-P-O	Highly reactivatable	Log P <2.0
Coumaphos	036501	56-72-4	3: P=S; P=O; S-P-O	Highly reactivatable	Log P >4.0
Terbufos	105001	13071-79-9	4: P=S; P=O; S-P-S; S-P-O	Highly reactivatable	Log P >4.0
Profenofos	111401	41198-08-7	2: P=O; S-P-O Et & n-Pr Groups	Highly reactivatable	Log P >4.5
Bensulide	009801	741-58-2	3: P=S; P=O; S-P-S; S-P-O; iPr Groups	Highly reactivatable	Log P >4.0
Diazinon	057801	333-41-5	3: P=S; P=O; S-P-O	Highly reactivatable	Log P: 3.81
Ethoprop	041101	13194-48-4	3: P=O; S-P-S; S-P-O; Et & nPr Groups	Highly reactivatable	Log P: 3.60
Dimethoate	035001	60-51-5	4: P=S; P=O; S-P-S; S-P-O	Highly reactivatable	Log P: 0.80
Malathion	057701	121-75-5	2: P=O; P=S; S-P-S	Highly reactivatable	Log P: 2.4
Phosmet	059201	732-11-6	4: P=S; P=O; S-P-S; S-P-O	Highly reactivatable	Log P: 2.9
Chlorethoxyfos	129006	54593-83-8	3: P=S; P=O S-P-O	Highly reactivatable	Log P: 4.59
Acephate	103301	30560-19-1	3: P=O; S-P-O; N-P-O	Highly reactivatable	Log P; -0.9
Methamidophos	101201	10265-92-6	3: P=O; S-P-O;N-P-O	Highly reactivatable	Log P: -0.8
Pirimiphos-methyl	108102	29232-93-7	3: P=S; P=O S-P-O	Highly reactivatable	Log P: 4.12
TCVP	083701	961-11-5	1: P=O	Highly reactivatable	Log P: 3.53

Tribufos	074801	78-48-8	2: P=O; S-P-O; n-Bu Groups	Highly reactivatable	Log p: 5.7
Phorate	057201	298-02-2	3: P=S; P=O S-P-S	Highly reactivatable	Log P: 3.56
Phostebupirim	129086	96182-53-5	3: P=S; P=O S-P-S	Highly reactivatable	Log P: 4.2
DDVP	084001	62-73-7	1: P=O	Highly reactivatable	Log P: 1.2
Naled	034401	300-76-5	1: P=O	Highly reactivatable	Log P: 2.18
Trichlorfon	057901	52-68-6	1: P=O	Highly reactivatable	Log P: 0.6
Fenamiphos	100601	22224-92-6	1: P=O	Highly reactivatable	Log P: 3.3
AZM	058001	86-50-0	4: P=O; P=S S-P-S; S-P-O	Highly reactivatable	Log P: 2.46
Methidathion	100301	950-37-8	2: P=O; P=S S-P-S	Highly reactivatable	Log P: 2.20
Propetamphos	113601	31218-83-4	3: P=S; P=O S-P-O	Highly reactivatable	Log P: 3.82
ODM	058702	301-12-2	2: P=O; S-P-O	Highly reactivatable	Log P: -0.74
Disulfoton	032501	298-04-4	3: P=S; P=O S-P-O	Highly reactivatable	Log P: 4.02
Methyl parathion	053501	298-00-0	3: P=S; P=O; S-P-O	Highly reactivatable	Log P: 2.86
Temephos	059001	3383-96-8	3: P=S; P=O; S-P-O	Highly reactivatable	Log P: 5.96
Chlorpyrifos-methyl	059102	5598-13-0	3: P=S; P=O: S-P-O	Highly reactivatable	Log P: 4.31

Highlights to consider in Review of Table 2- These physical organic chemistry concepts highlight the Agency's nonscientific interpretation of epidemiological studies without any recourse to proof of exposure, or consistency between imprecise exposure information and established biological mechanism of action and hazard outcomes:

- The DAP fingerprint mixtures of individual OPs and their stoichiometries, coupled with systemic exposure surrogates such as log P and aging potentials are illustrated in the Table above.
- Following OP inhibition of AChE, the phosphorylated enzyme can be spontaneously reactivated through the mediation of biological fluid hydrolysis. The exogenous correlate is treatment with strong nucleophiles such as oximes. The phosphorylated enzyme can also undergo an irreversible aging process during which the OP-Enzyme conjugate is cleaved at a site away from the binding site – rendering reactivation impossible.
- Fat soluble OPs such as chlorpyrifos and methyl parathion, etc. have a delayed passage to the nervous system, but can redistribute from adipose tissues over time. The reactivation potential of AChE is thus further increased since only manageable systemic levels are available to interact with the enzyme in real time.
- All OPs in this list have a high reactivation potential and thus have a lower hazard level of concern. Compounds with enzyme inhibitor complex that can be aged show higher hazard levels of concern. These distinctions cannot be captured by simple measures of non-specific urinary DAPs or epidemiological studies with imprecise exposure identities and /or metrics.
- Some cholinesterase inhibitors have delayed onset and hence the reactivation potential of their enzyme inhibitor complex is high. This is because they must first be metabolically converted to the active form or forms. Examples include methyl parathion, malathion, and methidathion.
- In line with the pentavalency of phosphorus within OPs, there are chemically defined mixtures of DAPs – coupled with defined ratios of each DAP— that serve as exposure fingerprints for each individual OP. Without these concordant stoichiometries, these urinary DAP assays are not scientifically interpretable.

4. Animal studies for OPs have been specifically designed and adopted by international regulatory agencies to evaluate the cause and effect of a single chemical, at various dose levels, under various routes of exposure and replicated in other rigorously designed studies. The Columbia Cohort, Mt. Sinai, and CHAMACOS studies were not designed to evaluate the association between OP exposure and neurodevelopmental outcomes for use in risk assessment. Animal studies are focused on a single OP compound of exposure in a highly controlled environment, holding all other environmental factors steady so that the relationship between OPs and health effects can be clearly established. For example,

the exposure assessment cannot address OPs that originate from different sources nor differentiate effects that may be attributed to other chemical exposures (e.g., lead), or human drugs (e.g., cyclophosphamide).

5. Extensive mechanistic data demonstrate that the adverse initiating event for OPs (cholinesterase inhibition) is an SN2 (substitution nucleophilic bimolecular) type biochemical reaction. Under the conditions of these Studies, which the Agency stated were likely conducted following significant residue declines, a scientifically relevant alternative hypothesis worth considering is that SN1 (substitution nucleophilic unimolecular) type processes are operative in current conditions of exposure. Biologically, these represent the multiple and diurnally variable occurrences of apical endpoints seen in random populations, in the absence of any external stimuli.

   A credible alternative hypothesis based on this mechanistic shift is that the observations in the human epidemiological data represent random events without any linkage to specific OP exposure as a stimulus or causal agent. The Literature Review includes multiple examples of non-statistically significant odds ratios incorrectly blended together by the Agency to create a semblance of false consistency, which, in turn, is used to construct an unstable platform for its unsupported conclusion. Statistical significance is determined when the 95% confidence interval excludes the null value and/or the p value is less than 0.05. The Agency failed to communicate the difference between risk estimates with and without statistical significance.

6. Missing from the Literature Review are several studies that show no adverse associations of OP exposure and neurodevelopment (Cartier et al. 2015; Engel et al. 2015; Yolton et al. 2013). Specifically, the Agency fails to address the Cincinnati Children's Environmental Health Center HOME Study. In an evaluation of the pooled data from the HOME, Columbia Cohort, Mt. Sinai, and CHAMACOS studies published by the authors of pooled data from the four studies, it becomes evident that the results are not consistent (Engel et al. 2015). This joint publication suggests that the results of the CHAMACOS study are an outlier and that the HOME study shows a positive association between DAP urine levels and the Mental Developmental Index (MDI) in 24-month olds. EPA's exclusion of negative studies, compounded by inherent publication bias, shifts the weight of evidence in favor of inappropriately inflating any suggested associations between OP exposure and neurodevelopmental effects.

7. EPA's results from Developmental Neurotoxicity Testing (DNT) studies conducted in compliance with EPA guideline 870.6300 and Good Laboratory Practice (GLP) standards

appear to be dismissed while results from published literature (without access to the raw data) are afforded greater weight. Overall, findings reported in the open literature showed mixed and inconsistent results, which might be attributable to differences in routes of administration, dosing regimen, vehicle or test methods employed, assessment criteria utilized, etc. For these reasons, the inconsistencies across open literature studies should not be integrated with the GLP studies submitted by OP registrants.

Of the 19 literature studies identified by EPA, seven involved subcutaneous administration of an OP to animals in dimethyl sulfoxide (DMSO). The kinetic and neurobehavioral properties of DMSO present a significant confounding variable when neurotoxicity and neurodevelopment are the key endpoints of evaluation/investigation. Studies have shown that intraperitoneal injection administration of dilute solutions of DMSO can have a significant impact on the nervous system (Cavaletti et al., 2000). Other authors also have shown that DMSO used as a dose vehicle also can modify and enhance the clinical symptoms of OPs (Ballough et al. 2008; Carr et al. 2008). Therefore, the presentation of adverse effects may be due to a combination of route of exposure (subcutaneous administration) and confounding by the dose vehicle, DMSO.

Appendix C- FQPA Considerations

1. The FQPA Safety Factor provision is intended to "take into account potential pre and postnatal toxicity and completeness of data with respect to exposure and toxicity to infants and children." EPA guidance for applying the FQPA Safety Factor provision, as it relates to determining the safety of a factor different from the default 10X FQPA SF, directs scientists in performing both aggregate and cumulative risk assessments to consider a three-part framework that focuses on each of these elements (USEPA, 2002b):

    - **The completeness of the database-** The database 10X uncertainty factor may be applied to address missing studies that pertain to susceptibility of the young.

    - **The potential for pre- or postnatal toxicity in infants and children-** Several lines of evidence should be taken into account such as the type of pre- and postnatal toxicity observed, the nature of the dose response, information on the toxicokinetics, and data on mode of action (MOA).

    - **The completeness of the exposure database-** The Agency should consider whether there are sufficient data (includes data strength/weakness) on the magnitude of potential exposure.

    In addressing these three elements, the FQPA analysis for cumulative risk assessment focuses on providing protection from the common toxic effect that could result from all pertinent routes and pathways of exposure to the members of the group that share the common mechanism of toxicity.

2. The Agency's thorough evaluations of the sensitivity and susceptibility to the mechanism of toxicity of the organophosphates articulated in the FIFRA SAP report "*Determinations of the Appropriate FQPA Safety Factor(s) in the Organophosphorus Pesticide Cumulative Risk Assessment*" (USEPA, 2002a) are contradicted by the recent assumptions made by the Agency that human epidemiological studies alone can raise sufficient uncertainty that adverse neurodevelopmental effects are occurring at levels below 10% inhibition of acetylcholinesterase to warrant a 10X FQPA Safety Factor. In 2002, the Agency concluded that "Because AChE inhibition is the mechanism of toxicity and precursor event to toxicity, functional effects in the young that result from inhibition of AChE activity should not occur at doses lower than those causing AChE inhibition."

3. The Studies[8] cited by EPA as the basis for retaining the 10X FQPA Safety Factor establish only a correlation between OP exposure and neurodevelopmental effects at best. Not only do the Studies fail to establish any causal relationship, but the Agency must be reminded that it previously determined that such a relationship of neurodevelopmental effects in the absence of AChE inhibition is not biologically plausible. The Agency's recent action based on these Studies presents itself as a complete reversal of scientific confidence.

4. The Agency must demonstrate that the decision to retain a full 10X FQPA SF, despite the rich database of animal toxicity and mechanistic data, is warranted based on scientifically credible and reliable data. The mode of action supported in the animal and human data of inhibition of acetylcholinesterase has been and continues to be the most scientifically based endpoint for the human health risk assessment. In comparison to the Studies, the animal data are clearly more robust and have undergone many scientifically rigorous levels of expert peer review. Until the Agency acquires access to the raw data, and an expert panel of epidemiologists and risk assessors is convened to perform all necessary analyses to confirm and replicate the findings and ensure that all data have been appropriately evaluated, EPA's proposed retention of a 10X FQPA SF is premature and not warranted.

[8] Throughout these appendices, "Studies" refers three major U.S based prospective birth cohort studies: (1) Mothers and Newborn Study of North Manhattan and South Bronx conducted by Columbia University, or the "Columbia Study/Cohort;" 2) Mount Sinai Inner-City Toxicants, Child Growth and Development Study, or the "Mount Sinai Study/Cohort;" and 3) Center for Health Assessment of Mothers and Children of Salinas Valley (CHAMACOS) conducted by the University of California Berkeley, or "CHAMACOS Study/Cohort." "Literature Review" refers to EPA's 2015 Literature Review on Neurodevelopment Effects and FQPA Safety Factor Determination for the OPs.

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