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

April 8 2016

Re: Meetings: FIFRA Scientific Advisory Panel (FIFRA SAP) to consider and review Chlorpyrifos: Analysis of Biomonitoring Data, March 8, 2016; FR Doc No: 2016-05174; Docket ID: EPA-HQ-OPP-2016-0062-0001.

To Whom It May Concern,

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 March 8, 2016, EPA provided Notice for a 3-day meeting of the Federal Insecticide, Fungicide, and Rodenticide Act Scientific Advisory Panel ("FIFRA SAP" or "SAP") to consider and review "Chlorpyrifos: Analysis of Biomonitoring Data." 81 Fed. Reg. 12099 [Docket ID: EPA-HQ-OPP-2016-0062-001]. CLA does not support convening the FIFRA SAP at this time. As requested in the CLA April 5 2016 letter,¹ in support of the AMVAC and Dow AgroSciences Petitions to postpone the SAP, convening of this SAP is premature. We strongly encourage the Agency to postpone the FIFRA SAP scheduled for April 2016. If EPA is to deny the CLA request to postpone

¹ CLA support of AMVAC and DAS petitions to postpone the SAP (submitted to the EPA-HQ-OPP-2016-0062-0001 Docket on April 5, 2016).

the FIFRA SAP, we think it critical that the SAP know and understand the deficiencies in the studies reviewed and assumptions EPA made in using such studies for regulatory decisions.

It is Premature for EPA to Consider Using Outcomes of Epidemiological Studies as its Foundation for Analysis and Review of Biomonitoring Data

In 2010, EPA posted for comment a *Draft Framework for Incorporating Human Epidemiologic & Incident Data in Health Risk Assessment*. The Draft Framework was created to guide the Agency's use of epidemiological data in assessing risk, but in that draft, EPA itself acknowledged the risks and limitations of relying on epidemiological studies for regulatory decision-making. For instance, the Draft Framework report notes:

“...there are several important factors to consider when evaluating epidemiologic studies including their goals, study population, characterization of exposure, ascertainment of disease, consideration of bias and confounding, and data collection, analysis, and documentation. Due to these factors, the size, scope, and quality of epidemiology studies can vary significantly. Ultimately these factors will determine the impact of epidemiologic findings on pesticide risk assessment and risk management decisions. Therefore, it is important to evaluate the strengths and limitations of epidemiologic studies when incorporating epidemiologic findings into risk assessment.”

Six years after seeking public comment on the Draft Framework, EPA has not yet responded to the multitude of comments expressing scientific concern with the use of epidemiological data in risk assessment, and has not finalized the Draft Framework. Yet, EPA appears to be using specific epidemiological data from the Columbia Study, incorporating those data into human health risk assessments, and recommending policy changes² with the potential to greatly impact pesticide registrations and re-registrations.

The Agency intends to use outcomes from epidemiological studies from three major U.S.- based prospective birth cohort studies reported in publications of study outcomes : (1) Columbia University (“Columbia Study”);³ (2) “Mount Sinai Study/Cohort;”⁴ and, (3) “CHAMACOS Study”⁵

² USEPA. 2015. Literature review on neurodevelopment effects and FQPA Safety Factor determination for the organophosphate pesticides (Literature Review).

³ 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.

⁴ 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.

⁵ 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.

(“the Studies”) as its foundation for analysis and review of chlorpyrifos biomonitoring data. The Agency’s use of the Studies is foundational for the charge questions issued to the SAP as it deliberates on the potential health impacts of chlorpyrifos exposure. CLA contends, however, that use of these Studies is premature because EPA has failed to address significant scientific questions on the propriety of using the Studies identified through prior FIFRA SAPs. Further, EPA has failed to address similar questions posed to it through public comment on its 2010 *Draft Framework for Incorporating Human Epidemiologic & Incident Data in Health Risk Assessment* (Draft Framework).⁶ EPA convened two FIFRA SAPs (2008⁷ and a 2012⁸) to address scientific questions associated with the use of a Columbia Study database for purposes of quantitative risk assessment and specifically for use in ascribing an association between the chlorpyrifos ‘exposure’ measures reported with any human health outcomes or impacts. Both SAPs expressed serious concern about the utility of the underlying data in the Columbia Study and posed questions to EPA about these concerns. To date, EPA has not addressed the concerns posed by the 2008 and 2012 SAPs. We object to EPA convening the 2016 FIFRA SAP given the unaddressed questions.

This shift in approach to use of epidemiological data in human health risk assessment is precedent setting. The underlying assumptions EPA makes regarding use of epidemiological data garnered from the 2008 and 2012 SAPs, the 2010 Draft Framework, and as expressed in the 2015 Literature Review, have not been validated and EPA has provided no response to any of the comments from affected stakeholders regarding these documents. We think it important that the SAP be made aware of these missing elements, making it premature for EPA to seek guidance from this SAP.

The Studies were not Designed to Document “Cause and Effect” Relationships

The Agency intends to use outcomes from the Studies as its foundation for analysis and review of chlorpyrifos biomonitoring data. However, these “outcomes” published in open literature do not represent primary data from any of the Studies. Nevertheless, the Agency’s use of the Studies is foundational for the charge questions issued to the SAP as they deliberate on the potential health impacts of chlorpyrifos exposure. How can the charge questions be objectively addressed when the Studies’ primary data are not available for verification? How the existing

⁶ USEPA. Office of Pesticide Programs. 2010. Draft Framework for Incorporating Human Epidemiologic and Incident Data into Human Health Risk Assessment.

⁷ USEPA. Office of Prevention, Pesticides, and Toxic Substances. Office of Science Coordination and Policy. FIFRA Scientific Advisory Panel, 2008

⁸ USEPA. Office of Prevention, Pesticides, and Toxic Substances. Office of Science Coordination and Policy. FIFRA Scientific Advisory Panel, 2012. “Chlorpyrifos Health Effects.”

charge questions for the 2016 FIFRA SAP⁹ are answered may likely establish policy for a human health risk assessment approach during pesticide registration review. This shift could occur without the Agency or the SAP addressing fundamental flaws in the Studies, and therefore flawed assumptions on which such policy could rest.

For these reasons, a crucial SAP charge question should precede any consideration of the existing charge questions posed to the 2016 FIFRA SAP.¹⁰ EPA should propose the SAP to first consider:

“Can these epidemiological studies be appropriately used for risk assessment purposes?”

We posit that the answer is “no.” Either in response to the proposed charge questions, or as a foundation on which the SAP responds to the current charge questions, CLA urges the SAP to consider the following aspects of epidemiological data evaluation for risk assessment purposes.

In the 2012 FIFRA SAP review of “Chlorpyrifos Health Effects,” the notes from the meeting state, “[T]hese three epidemiological 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.”¹¹ We strongly agree with this conclusion, and accordingly, the Studies should not be the basis for the quantitative risk assessment that underlies the hypotheses and charge questions posted for consideration during the 2016 FIFRA SAP. In its 2016 SAP background and charge document, EPA notes that in the 2008 and 2012 FIFRA SAPs, the Agency was cautioned against using the biomonitoring data from the Studies, particularly the Columbia Study, to directly derive point of departure (PoD). This caution was based on the SAP’s conclusion that there are uncertainties associated with lack of knowledge about timing of indoor chlorpyrifos applications and a single measure of exposure (cord blood) collected. While the 2012 SAP acknowledged the value of the data, it urged the Agency to ‘find ways to use the epidemiology studies.’

These Studies were not designed to demonstrate cause of any human health impact and the effect of exposure to any singular compound. The Studies do not investigate environmental

⁹ USEPA. Office of Prevention, Pesticides, and Toxic Substances. Office of Science Coordination and Policy. FIFRA Scientific Advisory Panel, 2016. Chlorpyrifos: Analysis of Biomonitoring Data.” Charge to the FIFRA SAP for the April 19-21 2016 Meeting.

¹⁰ USEPA. Office of Prevention, Pesticides, and Toxic Substances. Office of Science Coordination and Policy. FIFRA Scientific Advisory Panel, 2016. Chlorpyrifos: Analysis of Biomonitoring Data.” Charge to the FIFRA SAP for the April 19-21 2016 Meeting.

¹¹ USEPA, Office of Prevention, Pesticides, and Toxic Substances. Office of Science Coordination and Policy. FIFRA Scientific Advisory Panel, 2012. “Chlorpyrifos Health Effects” at 50. (“2012 SAP Minutes”). <http://www2.epa.gov/sites/production/files/2015-06/documents/041012minutes.pdf>

factors correlated with any environmental exposure that could result in any cause and effect relationship identified.

Gaps identified in the design of these Studies include:

- Blood and urine analyses represent only single points of time;
- No timeline for any exposure to chlorpyrifos is reported; no linkage between any exposure and an analytic outcome has been made;
- Not all data reported for chlorpyrifos represent a direct measure of chlorpyrifos. Non-specific pesticide exposure measurements (in Mt. Sinai and CHAMACOS studies) do not directly reflect any exposure to chlorpyrifos;
- Exposure measurements do not account for any potential impact of food or water consumption;
- Multiple chemical exposures are not controlled in the data analyses;
- The populations studied in all three cohorts are not representative of the general population; and,
- It is unclear which variables are controlled in the risk assessments, potentially resulting in confounding analyses.

Furthermore, in the absence of access to primary data, there is no means by which to validate the reported findings. Because of these significant gaps, the Studies should not and cannot be used to establish a causal relationship between chlorpyrifos exposure and neurodevelopmental outcomes. The decades-long tool for assessment of any impact of chlorpyrifos (and other organophosphates) on health is acetylcholinesterase (AChE) inhibition. It is important to note that researchers who have reviewed the outcomes from the Studies reported equivocal evidence of adverse human health effects associated with exposure levels below AChE inhibition (Burns et al. 2013¹²; Eaton et al. 2008¹³; Li et al. 2012¹⁴; Prueitt et al. 2011¹⁵; Reiss et al. 2015¹⁶). Nevertheless, the Agency now is suggesting that these data do in fact demonstrate adverse human health outcomes with exposure levels that do not impact AChE activity. The

¹² Burns C. J., McIntosh L. J., Mink P.J., Jurek A.M., Li A.A., 2013. "Pesticide exposure and neurodevelopmental outcomes: Review of the epidemiologic and animal studies," *J Toxicol Environ Health B Crit Rev* (16:3-4), pp 127-283.

¹³ Eaton D.L., Daroff R.B., Autrup H., Bridges J., Buffler P., Costa L.G., Coyle J., McKhann G., Mobley W.C., Nadel L., Neubert D., Schulte-Hermann R., and Spencer P.S., 2008. "Review of the toxicology of chlorpyrifos with an emphasis on human exposure and neurodevelopment," *Crit Rev Toxicol* (38 Suppl 2), pp 1-125.

¹⁴ Li, A.A., Lowe, K.A., McIntosh, L.J., and Mink, P.J., 2012. "Evaluation of epidemiology and animal data for risk assessment: chlorpyrifos developmental neurobehavioral outcomes," *J Toxicol Environ Health B Crit Rev* (15:2), pp 109-184.

¹⁵ Prueitt R.L., Goodman J.E., Bailey L.A., and Rhomberg L.R., 2011. "Hypothesis-based weight-of-evidence evaluation of the neurodevelopmental effects of chlorpyrifos," *Crit Rev Toxicol* (41:10), pp 822-903.

¹⁶ Reiss R., Chang E.T., Richardson R.J., Goodman M., 2015. "A review of epidemiologic studies of low-level exposures to organophosphorus insecticides in non-occupational populations," *Crit Rev Toxicol* (45:7), pp 531-641.

Agency is proposing that a new mechanism of action is likely, and the point of departure for assessment of negative impact is changed from the historic AChE inhibition marker. These assumptions are not supported by validated study data. In fact, those primary data are not available for validation. Such assumptions contradict many decades worth of animal testing and data development with studies supported by EPA-required toxicological studies designed to test such hypotheses. This unprecedented change in approach greatly affects the testing paradigm for human health impacts of organophosphates and potentially many other classes of compounds in the future.

Recent publications (Cartier et al. 2015¹⁷; Engel et al. 2015¹⁸; Yolton et al. 2013¹⁹) indicate that EPA has conducted an incomplete review of published epidemiological study outcomes. Missing from the EPA assessment is any discussion of publications reporting no adverse association between organophosphates and neurodevelopment. Exclusion of negative studies inappropriately shifts the weight of evidence supporting any impact, and inflates any potential relevant association between chlorpyrifos exposure and neurodevelopmental effects.

If risk assessments are to integrate epidemiological data sets, a well-established, systematic balance between the weights afforded observational human epidemiological studies compared to harmonized test guidelines for animal toxicity testing that are specifically designed for risk assessments must first be developed. In addition, when data conflicts and decisions must be made, more robust data must be used over data of lesser validity. Other data, such as epidemiological data, may form a basis for additional investigation, but it cannot be afforded greater weight than high-quality guideline studies specifically designed for regulatory use. To do so would result in serious damage to the scientific credibility of EPA risk assessments.

Epidemiological Findings from the Columbia Study have Inherent Limitations when used in Risk Assessment

In its Draft Framework EPA refers to use of a modified Bradford Hill²⁰ criteria approach to assessing strength and appropriate use of epidemiological studies in human health risk assessment. The criteria support sound approaches to evaluating associations in

¹⁷ Cartier C., Warembourg C., Le Maner-Idrissi G., Lacroix A., Rouget F., Monfort C., Limon G., Durand G., Saint-Amour D., Cordier S., and Chevrier C., 2015. "Organophosphate insecticide metabolites in prenatal and childhood urine samples and intelligence scores at 6 years of age: Results from the Mother-Child PELAGIE Cohort (France)," *Environ Health Perspect* Sep 22 (epub ahead of print).

¹⁸ Engel S. M., Bradman A., Wolff M. S., Rauh V.A., Harley K.G., Yang J.H., Hoepner L.A., Barr D.B., Yolton K., Vedar M.G., Xu, Y., Hornung R.W., Wetmur J.G., Chen J., Holland N.T., Perera F.P., Whyatt R.M., Lanphear B.P., Eskenazi B., 2015. "Prenatal organophosphorus pesticide exposure and child neurodevelopment at 24 Months: An analysis of four birth cohorts," *Environ Health Perspect* Sep 29

¹⁹ Yolton K., Xu Y., Sucharew H., Succop P., Altaye M., Popelar A., Montesano M.A., Calafat A.M., Khoury J.C., 2013. "Impact of low-level gestational exposure to organophosphate pesticides on neurobehavior in early infancy: A prospective study," *Environ Health* (12:1), pp 79.

²⁰ Hill A. B., 1965. "The environment and disease: Association or causation?," *Proc R Soc Med* 58, pp 295-380.

epidemiological data cohorts but are not intended to be used to establish a cause and effect association between exposure and health or environmental impact. It is important to note that even when primary data are available for statistical reassessment, epidemiological studies are not intended to replace toxicological data collected from animal studies intended to establish effects in studies. The Columbia Study, as the primary example, does not provide a basis for contending that there is an association between chlorpyrifos and human health outcomes; nor does it demonstrate a response to a specific exposure. These Studies were not designed to support a hypothesis to demonstrate a causal relationship with any of the variables studied; any relationship is an association although none of the associations reported were statistically significant.

The 2012 SAP report states, “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...”²¹

Specifically, limitations existing in the Columbia Study that limit its usefulness in risk assessment include:²²

- Inability to generalize any adverse outcome reports from the study subpopulation
- Analytical methods are unknown; the accuracy cannot be accurately related to chlorpyrifos exposure;
- Limited sample size does not provide robust study outcomes that could be useful in quantitative risk assessment;
- The plausibility of a biological mode of action is not established;
- Replication or verification of the study outcomes is not possible as the data represent specific points in time with a targeted populations; and,
- The maternal and cord blood analyses each represent one sample, collected at one point in time—at birth and with no corresponding information regarding the environmental conditions of the home during pregnancy; thus, no exposure levels can be determined for the mothers or their infants.

²¹ USEPA, Office of Prevention, Pesticides, and Toxic Substances. Office of Science Coordination and Policy. FIFRA Scientific Advisory Panel, 2012. “Chlorpyrifos Health Effects” at 19, 50.

<http://www2.epa.gov/sites/production/files/2015-06/documents/041012minutes.pdf>

²² Dow AgroSciences comments to Revised Human Health Risk Assessments: Chlorpyrifos Registration Review; Extension; January 14, 2015; Docket ID: EPA-HQ-OPP-2008-0850-0224 at 11, 80

<https://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPP-2008-0850-0845> .

In order for any verification of the Studies' outcomes to be possible, the primary data from the Studies are needed. However, since such raw data are not available, it is not possible to replicate the Studies' findings; independent statistical assessment of the data is not possible. EPA's reliance on the Studies, where all raw data are not available, belies EPA's own standards imposed on registrants (e.g., the robust data quality assurance required by Federal guidelines in 40 CFR Part 160) and EPA data quality guidelines for federally-funded studies.^{23,24} CLA questions the use of information reported or outcomes from these Studies since there is not a means by which those outcomes can be verified, validated or replicated without Agency access to the data from the Studies.

Conclusion: Convening of this FIFRA SAP is Premature

CLA strongly encourages EPA to postpone the SAP so that a critical review of the Studies' outcomes and data can be appropriately conducted. As the above discussion shows, it is scientifically and procedurally unprecedented for the Agency to convene an SAP premised on EPA's use of the Studies and unprecedented to use the Studies to set the foundation for the charge questions to the SAP.

Without transparent access to all data generated for public review, and without publication of the Agency approach to use of epidemiological study outcomes, such application of epidemiological data in quantitative risk assessment is premature. Toxicological data provided by registrants for EPA risk assessment have been submitted for decades. It is not scientifically valid to conduct a human health risk assessment, considering the strength of epidemiological and toxicological studies, and ignore primary data submitted to EPA during pesticide registration. These toxicological study data, documenting safe levels of use for each active ingredient are specific to the pesticide ingredients while no such epidemiological data are available for review and validation.

CLA submitted a petition to EPA to request that the SAP be postponed. It is not possible to fully evaluate the outcomes from the Columbia Study; and in the absence of any EPA response to significant questions the two previous SAP directed to the Agency, we do not consider any charge questions posed to the 2016 FIFRA SAP to be appropriate. Nothing has changed as to access to data from the Columbia Study, EPA's process for integration of epidemiological data, or how an appropriate weight of evidence for risk assessment has been used. It is not clear what is new for SAP deliberation. If new data are available, those data must be made known with opportunity for public comment.

²³ See Dow AgroSciences comments to Revised Human Health Risk Assessments: Chlorpyrifos Registration Review; Extension; January 14, 2015; Docket ID: EPA-HQ-OPP-2008-0850-0224 at 11, 23, 34 and 39

²⁴ See Dow AgroSciences comments to Chlorpyrifos; Tolerance Revocations; 80 FR 69080; November 6, 2015; Docket ID: EPA-HQ-OPP-2015-0653 ("Dow Tolerance Comments") at 11, 18, and 19
<https://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPP-2015-0653-0266>

* * *

CLA appreciates your consideration of and attention to these comments, and the potential implications of oversights in information sharing for chlorpyrifos and other compounds.

Please direct any questions for CropLife America to Dr. Tamika Sims (tsims@croplifeamerica.org).

Regards,

A handwritten signature in black ink that reads "Tamika D. Sims". The signature is written in a cursive, flowing style.

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