November 29, 2016

Dr. Jack Housenger
United States Environmental Protection Agency
Director, Office of Pesticide Programs
2777 Crystal Drive
One Potomac Yard South
Room 12621
Arlington, VA 22202-3553

Sent via email

Re: Petition EPA to halt regulatory decisions that are highly influenced/determined by results of epidemiological studies that do not meet well-defined data quality standards, and that are not integrated into the health risk assessment in a transparent, well-defined manner

Dear Director Housenger:

Enclosed please find a CropLife America (CLA) Petition to the US Environmental Protection Agency (EPA) to suspend any regulatory decision making on human health risk assessment(s) for organophosphate and other pesticides, using an FQPA 10X Safety Factor supported principally by the use of epidemiologic studies that generally do not meet well-defined data quality standards, and specifically are heavily weighted on the Columbia Study outcomes.

CropLife America is the not-for-profit trade organization representing the nation's developers, manufacturers, formulators and distributors of plant science solutions for agriculture and pest management in the United States. Our member companies produce, sell and distribute virtually all the crop protection technology products used by American farmers and other consumers. We are committed to the safe and responsible use of the industry's products in order to provide safe and abundant food, as well as to control insect and plant disease vectors for the protection of human health, all providing valuable benefits to the agriculture, farmers and the consumer.

The Petition requests EPA to cease regulatory decision making, specifically with respect to the organophosphate pesticides, until EPA has transparently developed criteria for acceptance of epidemiologic studies in human health risk assessment, and guidance for integration of epidemiologic studies in pesticide risk assessment historically based on animal toxicological and *in vitro* studies.

Due to uncertainties within the regulatory environment created by the lack of such integration guidance, and the potential impact on the availability of crop protection products based on inappropriate selection and use of epidemiological studies by the EPA Office of Pesticide

Programs in its human risk assessments for pesticide registrations, CLA respectfully requests that you respond to our Petition within 45 days.

Should you have any questions regarding the CLA Petition, please contact me directly [jcollins@croplifeamerica.org (+1-202-833-4474)].

Respectfully submitted,

Janet E. Collins, Ph.D., R.D.
Executive Vice President
CropLife America

PETITION TO HALT REGULATORY DECISIONS DETERMINED BY RESULTS OF EPIDEMIOLOGICAL STUDIES THAT DO NOT MEET WELL-DEFINED DATA QUALITY STANDARDS AND THAT ARE NOT INTEGRATED INTO THE RISK ASSESSMENT IN A TRANSPARENT, WELL-DEFINED MANNER

CropLife America (CLA) petitions the Environmental Protection Agency (EPA or the Agency) to halt any regulatory decisions on any organophosphate pesticide (OP), where that action is based primarily on results from highly influential studies that do not meet well-defined data quality standards, where the use of such a study is a determinative factor, yet the public has no means of knowing how EPA is determining the data quality of such a study and how it is being integrated into the risk assessment when its conclusions are not consistent with results from more traditional, and required testing. EPA's reliance on the Columbia Center for Children's Environmental Health epidemiology cohort studies of inner-city mothers and children (the Columbia Study) concerning pre- -natal pesticide exposure to chlorpyrifos to drive regulatory decisions is an example of this.

Established in 1933, CLA represents the developers, manufacturers, formulators and distributors of plant science solutions for agriculture and pest management in the United States. CLA's member companies produce, sell and distribute virtually all the vital and necessary crop protection and biotechnology products used by farmers, ranchers and landowners. Crop protection products are necessary to ensure safe, predictable and adequate supplies of food, fiber and fuel. CLA members support science-based regulation of pesticides to ensure that these products can be used without causing unreasonable adverse effects to either human health or the environment.

STATUTORY AND REGULATORY BACKGROUND

No pesticide product can be distributed or sold for use in the United States unless it has been registered by EPA under the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA),

7 U.S.C. § 136 *et seq*. Through FIFRA, the EPA receives extensive hazard and exposure information that is used to evaluate the risks of pesticide products.

The 1996 Food Quality Protection Act (FQPA) amended FIFRA and the Federal Food Drug and Cosmetic Act (FFDCA), requiring EPA, when setting tolerances for pesticide residues on food, to make a safety finding that the pesticide can be used with "a reasonable certainty of no harm" to human health. 21 U.S.C. § 346a(b)(2)(A). To meet this standard, EPA must consider (among other things) the special susceptibility of children to pesticides by using an additional tenfold (10X) safety factor (the Safety Factor) when setting and reassessing tolerances unless adequate data are available to support a different factor. *Id.*

EPA's human health pesticide risk assessment has traditionally relied on validated toxicological studies using laboratory animals along with data to estimate the potential exposure based on the proposed use of the pesticide product. Epidemiological studies of adverse effects in humans have not been uniformly or consistently incorporated into this quantitative risk assessment process, due to the observational nature of epidemiologic research, primarily due to questions related to study design, population studied, and lack of clear evidence of the magnitude and duration of exposure during critical phases of development and/or evidence of a dose-response relationship that would more clearly support a conclusion that exposure to a particular chemical may have caused an observable/measurable toxic effect, among other factors that would impact the use of epidemiologic study outcomes in quantitative risk assessment. While EPA has stated that epidemiological evidence, generically speaking, may provide important informative data for the risk assessment process, this determination does not mean that each and every published epidemiological study will provide equally important, valid or useful information. Like all information considered in a risk assessment, the quality and validity of the

information provided by epidemiological studies needs to be closely scrutinized before use in a regulatory risk assessment.

Through recent statements made by EPA in OP registration review dockets, EPA now seeks to change this process and incorporate unreliable and unverifiable epidemiological evidence directly into its pesticide risk assessment process through a framework that utilizes a weight of evidence approach, without explaining to the public how these studies, of varying quality, will be weighted when EPA does not have access to the raw data, and no criteria exist for either choice of study or integration of such data. EPA should cease further action on regulatory decision-making that finds epidemiological study results to be determinative until the Agency can establish criteria against which such study results can be evaluated, and clearly articulate how the Agency will determine the value added within the risk assessment in the context of the traditional empirical data.

EPA'S SHIFT IN APPROACH TO RISK ASSESSMENT

In January 2010, EPA published a Draft Framework for Incorporating Human Epidemiologic & Incident Data in Health Risk Assessment (the Draft Framework). The Draft Framework declares that "[EPA] intends to employ…epidemiology studies and human health incident data in its human health risk assessment" and that its "goal is to use such information in the most scientifically robust and transparent way." Draft Framework at 6. EPA based its decision to incorporate epidemiology into the risk assessment process on two reports issued by the National Research Council for the National Academy of Sciences, *Toxicity Testing in the 21st Century: A Vision and a Strategy* (2007) and *Science and Decisions* (2009). Per the Draft Framework, EPA expressed its intent to conduct human health risk assessments

that incorporate data from new sources, specifically information found in epidemiology studies, human incident databases, and biomonitoring studies.

In the Draft Framework, EPA sets forth a general plan for incorporating epidemiological studies into its risk assessment process and for weighing that evidence alongside traditional mechanistic and toxicological evidence in a weight of the evidence analysis. The Draft Framework describes the major types of epidemiological studies, noting the strengths and limitations of each in terms of their applicability to the risk assessment process. EPA's Draft Framework is premised on a proposed weight of the evidence evaluation that uses the modified Bradford Hill criteria as established in the Mode of Action Human Relevance Framework[1]; the framework serves as an approach for organizing and evaluating diverse types of data to determine the evidence available on the potential human health consequences of pesticide exposure.

In a critical failing, the Draft Framework did not set forth any criteria for selecting the epidemiological studies to be incorporated, or for evaluating the quality and validity of a particular epidemiological study to determine whether that study should be used in an EPA risk assessment in the first place, in spite of the fact that in its own guidance on use of open literature data for human health risk assessment, and the data quality guidance, EPA stated that it would work with the public (including the regulated community) to develop these criteria. Toxicological and exposure studies, in contrast, generally must meet strict design and "good laboratory practice" quality criteria and disclose all analyses for consideration during registration or registration review processes. *See e.g.*, 40 C.F.R. §§ 152.50, 158.80, and Part 160.

[1] A summary of EPA's Motion of Action Human Relevance Framework can be found at: https://cfpub.epa.gov/si/si_public_record_report.cfm?dirEntryId=246035.

As discussed in more detail below, a FIFRA Scientific Advisory Panel (2010 SAP) reviewed the Draft Framework at a meeting held in February 2010. While the 2010 SAP praised EPA for its use of the Bradford Hill criteria as the basis for how to incorporate epidemiology in a weight of the evidence analysis, the SAP strongly recommended that EPA establish a stringent set of quality-based criteria to determine whether to accept a given epidemiological study for use in risk assessment. FIFRA Scientific Advisory Panel Meeting Minutes No. 2010-03 at 10 (Feb. 2-4, 2010) (2010 SAP Minutes). Since the 2010 SAP meeting, CLA and its members have repeatedly requested an opportunity for input into such criteria; the Agency has continued to deny these requests, and has not issued the 2010 SAP-recommended criteria, despite have stated that it would work with the public to develop such criteria.

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).[2] The Draft Risk Assessments were intended to support the registration review of (1) a group of 22 pesticides known as sulfonylureas (not at issue here) and (2) seven OPs. CLA provided comments to each of the dockets contained within the overarching docket.[3] At that time, CLA also commented on the "Literature Review on Neurodevelopmental Effects and FQPA Safety Factor Determination for the Organophosphates" (the Literature Review) that was part of each of the seven OP dockets.[4] In the Literature Review EPA stated (buried on page 80 of 101) that it will be retaining the full 10X Safety Factor for *all*

[2] "Pesticide "Pesticide Registration Review; Draft Human Health and Ecological Risk Assessments for Sulfonylureas and Certain Other Pesticides; Notice of Availability and Request for Comment," 80 Fed. Reg. 57812 (Sept. 25, 2015), Docket No. EPA-HQ-OPP-2015-0386, available at: https://www.regulations.gov/searchResults?rpp=25&po=0&s=EPA-HQ-OPP-2015-0386&fp=true&ns=true.
[3] *See* Docket No. EPA-HQ-OPP-2012-0372-0066 (Sept. 12, 2016), available at: https://www.regulations.gov/docket?D=EPA-HQ-OPP-2012-0372; Docket No. EPA-HQ-OPP-2008-0345-0046 (March 3, 2016), available at: https://www.regulations.gov/document?D=EPA-HQ-OPP-2008-0345-0046.
[4] *See* EPA-HQ-OPP-2010-0119-0039 (February 22, 2016), available at: https://www.regulations.gov/document?D=EPA-HQ-OPP-2010-0119-0039.

OP pesticides. The Agency's stated rationale for retaining the full Safety Factor was based primarily on conclusions drawn from the Columbia Study, despite the fact that EPA has not evaluated, or even reviewed, the data underlying the Columbia Study's conclusions.

More recently, on November 10, 2016, the Agency issued a prepublication version of "Chlorpyrifos; Tolerance Revocations; Notice of Data Availability and Request for Comment."[5] In that document EPA states that it intends to revoke all food tolerances for the OP. That decision is based, at least in part, on applying the full 10X Safety Factor using the Columbia Study as the comparator for exposure levels considered to cause harm.

INTEGRATION OF DATA SOURCES IN HUMAN HEALTH RISK ASSESSMENT

Importance of Epidemiological Data in Risk Assessment

While EPA has stated that epidemiological evidence, generically speaking, may provide important informative data for the risk assessment process, this determination does not mean that each and every published epidemiological study will provide equally important, valid or useful information. Like all information considered in a risk assessment, the quality and validity of the information provided by epidemiological studies needs to be closely scrutinized.

Findings from properly conducted, high quality epidemiological studies may prove useful in characterizing and evaluating human health risks. But not all epidemiological evidence is created equal. Bias, confounding factors, and in particular, unreliable and invalidated exposure assessments commonly occur in epidemiological studies, limiting the value of the researchers' conclusions for quantitative risk assessments. In addition, a study's probative value varies dramatically depending on design and approach – observational studies, for instance, such as case series or ecological "cluster" analyses, do not carry the strength of association assessment

[5] https://www3.epa.gov/pesticides/PrePublicationCopy_16P-0280_2016-11-10.pdf

that prospective cohort and case control studies do and are often utilized only (if at all) for hypothesis generating purposes. *See* 2010 SAP Minutes at 20-21.

"Weight of evidence," in this context, requires more than mere consideration of "all" forms of epidemiological studies. The weight of evidence approach considers all relevant information in an integrative assessment that takes into account the kinds of evidence available, the quality and quantity of the evidence, the strengths and limitations associated with each type of evidence and explains how the various types of evidence fit together. *See* U.S. Environmental Protection Agency, A Summary of General Assessment Factors for Evaluating the Quality of Scientific and Technical Information, EPA 100/B-03/001 June 2003. Epidemiology studies used in risk assessments, thus, should report all analyses, negative or positive and provide all underlying data.

To date, EPA has provided no transparency regarding how it is judging the quality of epidemiological studies or weighing them against its traditional data requirements. Additional transparency and structure is needed before decisions are made based on this inscrutable evaluation.

EPA MUST ENSURE THE QUALITY OF DATA USED IN RISK ASSESSMENTS

The quality of scientific information forming the foundation for pesticide registration and use decisions is essential to all EPA risk assessments. For example, in 2002 EPA published "Guidelines for Ensuring and Maximizing the Quality, Objectivity, Utility, and Integrity of Information Disseminated by the Environmental Protection Agency," EPA/260R-02-008 (the Guidelines). EPA issued these Guidelines to formalize and maximize the quality of disseminated information, particularly with respect to the objectivity, utility, and integrity of scientific data. Under the Guidelines, information disseminated by EPA must be "presented in an accurate,

clear, complete, and unbiased manner" with substance that "is accurate, reliable, and unbiased." *Id*. at 15. Objectivity of influential scientific information is judged against the quality principles in the Safe Drinking Water Act Amendments (SDWA) of 1996 to ensure the use of (i) the best available science and supporting studies conducted in accordance with sound and objective scientific practices, including, when available, peer reviewed science and supporting studies; and (ii) data collected by accepted methods or best available methods (if the reliability of the method and the nature of the decision justifies the use of the data). *Id*. at 22.

Moreover, "influential" information, which is information that will have a clear and substantial impact on important public policies or private sector decisions, must "adhere to a rigorous standard of quality" and "should be subject to a higher degree of quality." *Id.* at 20. As noted in the Guidelines, information that can "adversely affect in a material way the economy, productivity, competition, jobs" or that addresses "precedent-setting or controversial scientific or economic issues" is considered influential. Because the overall economic impact on a currently registered pesticide of an EPA reassessment could be substantial, scientific data used to make those decisions would be influential. Unquestionably, epidemiological studies used in these risk assessments that impact registrations thus qualify as "influential" data subject to heightened quality standards under the Guidelines.

Requirements set out in the FQPA for setting tolerances mirror these guidelines. Under the FQPA, EPA must consider, among other relevant factors, the validity, completeness, and reliability of the available data from studies of the pesticide chemical. 21 U.S.C. § 346a.

CRITERIA FOR A WELL-DESIGNED, ROBUST EPIDEMIOLOGICAL STUDY

A well-designed, robust epidemiological cohort or case control study has certain features that OPP should look for before admitting a study into a risk assessment. These include, but are not limited to:

- well-characterized, quantitative exposure assessments that minimize measurement error, evaluates exposure during an etiologically relevant period, and decrease the likelihood of inaccurate or biased information;
- well-characterized, documented identification of disease and/or health status.
- a well-defined study population that includes persons with a wide range of exposures as well as unexposed persons; and
- documented efforts to control for selection bias, information bias and confounding; and
- full disclosure of the results of all statistical analyses conducted and models evaluated.

While quantitative criteria are a critical first step in separating reliable epidemiological studies from less reliable studies, an element of scientific judgment is required to make a complete assessment. To ensure a well-informed process, EPA must utilize the expertise of qualified epidemiologists to review the body of epidemiology evidence for a given pesticide to determine whether each study satisfies quality criteria. The 2010 SAP recommended several specific questions to be asked when evaluating each specific epidemiological study for potential use in a risk assessment. Those include:

1. Was the epidemiological study conducted primarily in a hypothesis- generating or a hypothesis-testing mode? Studies with no specific *a priori* hypothesis are more likely to generate false positive results.
2. Was the method of assessing exposure reliable and adequate?

3. Were inclusion and exclusion criteria clearly stated and reasonable to provide a representative sample with regard to exposure and health outcome so as to provide a relatively unbiased and representative estimate of effect?
4. Was the method of assessing the criteria for determining health outcome clearly stated and valid and reliable; e.g. confirmed with histopathology; and were they designed to detect newly diagnosed (rather than prevalent) cases so that it was reasonably possible to determine that exposure preceded disease?
5. Was appropriate information on potentially confounding factors, such as socio-demographic, behavioral and dietary factors collected for both exposed and unexposed groups or for cases and controls in the same way, and were they appropriately controlled in the analyses of the data? Were data on co-morbid conditions collected? (i.e. factors that are associated with the health condition of interest as well as factors associated with exposure)
6. Did the study sample the population or individuals of interest? (i.e. was selection bias minimized and generalizability optimized?) How does the study population relate to the universe of potentially exposed populations?
7. Did the study examine individuals with a wide range of exposures? (i.e. ability to detect a dose-response and to generalize to other populations). Did the study include unexposed populations or individuals?
8. Did the exposures examined in the study relate to past or current situations? (i.e. acute versus chronic exposures and the target health end points)
9. Did the study have adequate statistical power to detect meaningful differences for outcomes between the different groups of exposed and unexposed or less exposed

individuals while controlling for important confounding factors? Does the sample size take into account the expected incidence of the target health effect in the study populations? Was the study powerful enough to detect statistically meaningful differences while adjusting for confounding variables and exposure measurement error that typically reduce statistical power?

See 2010 SAP Minutes at 16-17.

NECESSITY OF THIS PETITION

It is undisputed that numerous high-quality animal toxicity studies on OPs have been conducted according to scientifically validated test methods and reviewed by the Agency in support of their registrations under FIFRA. The weight of evidence from these studies currently supports a highly conservative regulatory point of departure based on replicated Good Laboratory Practice studies in multiple species, durations and routes of exposure. Furthermore, the outcomes from these animal studies are aligned with and corroborated by standard physicochemical and mechanistic principles that have withstood the test of time. Thus, based on extensive laboratory data, EPA has moved away from the full 10X Safety Factor for OPs.

EPA has made a significant and fundamental change in the way it is applying the Safety Factor. As stated in the Literature Review and evidenced in the current OP draft risk assessments, EPA now intends to apply the full 10X Safety Factor to all OP pesticides, based primarily on conclusions drawn from the Columbia Study, although neither EPA nor the registrant have access to the data upon which this decision is based. Significant data quality inadequacies in the Columbia Study 'file' exist; and there is no indication of how EPA 'weighted' the Columbia Study results in any type of weight-of-evidence process, with no criteria for such approach. EPA's reliance on this study, in spite of significant and negative

comment and direction from three separate FIFRA SAPs is without precedent. Where are the data; what is the EPA response to the three SAP reviews and recommendations; and, most importantly, what is new in assessment of the Columbia Study publications since EPA began its assessment of chlorpyrifos that would support EPA changing its approach to assessment long after the Columbia Studies were published?

Such reliance violates both FIFRA and the FQPA and flies in the face of the Guidelines and 2010 SAP recommendations, discussed above. Neither EPA nor interested stakeholders, of which OP registrants are included, have been granted access to the Columbia Study's underlying data. Thus, EPA could not have adequately evaluated the data to determine its validity, completeness, and reliability, as required by the FQPA. The Agency has not confirmed that the data meets the quality criteria as recommended by 2010 SAP and it certainly does not meet the Guidelines' standard that information disseminated by EPA be "presented in an accurate, clear, complete, and unbiased manner" with substance that "is accurate, reliable, and unbiased." Because EPA's intended use of the Columbia Study meets none of the quality criteria required for epidemiological data use in pesticide risk assessment, EPA should not be allowed to make decisions based upon it.

For the reasons set forth here, CLA petitions EPA to cease further action on any regulatory decision-making based primarily on epidemiological studies until the Agency develops, and sets forth for public comment, data quality criteria for how these study results will be evaluated, weighed and integrated into the traditional data set required for pesticide risk assessment, consistent with the quality standards required by both Congress and EPA, itself.