13 February 2018

Mr. Christian Bongard
Pesticide Re-Evaluation Division (7508P)
Office of Pesticide Programs
Environmental Protection Agency
1200 Pennsylvania Ave. NW
Washington, DC 20460–0001

via Regulations.gov: **EPA–HQ–OPP–2012–0330-0083**

Re: Registration Review; Draft Human Health and/or Ecological Risk Assessments for Several Pesticides; Notice of Availability. Docket ID No. EPA–HQ–OPP–2012–0330-0083; 82 FR 59596; Dec 15, 2017.

Dear Mr. Bongard:

Established in 1933, CropLife America (CLA) represents the developers, manufacturers, formulators and distributors of crop protection chemicals and plant science solutions for agriculture and pest management in the United States. CLA's member companies produce, sell and distribute virtually all crop protection and biotechnology products used by American farmers. CLA represents interests of its member companies by, among other things, monitoring legislation, federal agency regulations and actions and litigation that impact 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 (herein EPA or the Agency), as the primary federal agency responsible for the regulation of pesticides, to encourage practical, risk-based regulation of its members' products.

On December 15, 2017, EPA made available for public comment its "Registration Review; Draft Human Health and/or Ecological Risk Assessments for Several Pesticides," including bamectin, buprofezin, chlorpropham, emamectin benzoate, fludioxonil, fluopicolide, fluridone, methiocarb, norflurazon, oryzalin, PBO (piperonyl buotoxide), pyriproxyfen, quinoxyfen, 2, 4-D, bifenthrin, and cyfluthrins. CLA and its member companies do not take issue with the conclusions reached, although we have some concerns with the method of incorporating data sources in a weight of evidence approach. We appreciate the opportunity to provide comments on the draft risk assessments, specifically referencing Docket ID No. EPA-HQ-OPP-2012-0330, 2, 4-D (Dichlorophenoxyacetic Acid) and the supporting documents, "Tier II Epidemiology Report (Non-Carcinogenic Effects Only)" and, "2, 4-Dichlorophenoxyacetic acid (2,4-D): Tier II Epidemiology Report (Carcinogenic Effects Only)."

I. EPA Regulatory Decision-Making Process

The Agency's process for evaluating epidemiological data, issued in the 2016 "Framework for Incorporating Human Epidemiologic & Incident Data in Risk Assessments for Pesticides," ("Framework"), and the release of the above-mentioned draft risk assessments for several pesticides, demonstrates inconsistent use of the public participatory process. Regulatory decisions made through an open and transparent government process are not mirrored in the recent actions of the Agency. The following points highlight Agency activity that should be addressed with corrective action:

The regulated and stakeholder communities expect sound scientific decisions made through a process that is methodical, evidence-based and data-driven. Deadlines should not take precedence over matters pivotal to protection of human health and the environment. The Agency should not be rushed to scientific judgement; it must take the requisite time and expertise to do a thorough risk-based scientific assessment.

The Agency has insufficiently communicated the way in which it considers using human epidemiological data now and in the future. The 2010 *Draft Framework for Incorporating Human Epidemiologic & Incident Data in Health Risk Assessment*, (Draft Framework), on how to consider human epidemiology and incident data in human health risk assessment was submitted to a Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) Science Advisory Panel (SAP) for review in 2010). The Agency finalized this document, but has yet to develop a "Response to Comment" document detailing how the Agency addressed each SAP recommendation or those made by the 2012 Federal Peer Review.

It is not clear that the Agency has consistently followed its peer review process in ensuring scientific rigor and transparency; uncertainty and lack of public confidence result from such a process that lacks transparency. In December 2016, the Agency released the final version of the "Framework for Incorporating Human Epidemiologic & Incident Data in Risk Assessments for Pesticides," ("Framework") without allowing or receiving public comments on that document.

CLA submitted comments on the EPA Docket for the FIFRA Scientific Advisory Panel on chlorpyrifos.[1] As part of its April 8, 2016[2] comments, CLA also provided input on the "Draft Framework for Incorporating Human Epidemiologic and Incident Data in Risk assessments for Pesticides" (Draft Framework). By reference, those comments are incorporated herein, with an extracted portion which follows:

> "*In its Draft Framework EPA refers to use of a modified Bradford Hill[3] 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 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*

[1]US EPA. 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-HQOPP-2016-0062-0001.

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

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."

CLA and its member companies continue to believe that a consistent and scientifically defensible approach to use of all sources of data in regulatory decision making is required. CLA does not support the approach taken in the EPA integration of literature, epidemiologic, and other sources of study outcomes its 2, 4-D draft human health risk assessment.

We believe it essential to underscore the need to consider recommendations from stakeholders, the 2010 SAP recommendations, and those from the 2012 Federal Peer Review; EPA must adhere to the scientific principles promoted in its "Framework" conclusions. To that end, CLA is submitting detailed comments to EPA Draft Human Health Risk Assessments involving epidemiological reviews for specific pesticides, as they become available.

The following comments and tables emphasize the lack of consistency in approach taken by EPA, relative to the recommendations in the "Framework."

II. Use of Epidemiology in Risk Assessments: 2, 4-D Registration Review Focus

The Revised Human Health Risk Assessment for Registration Review (RHHRA) for 2, 4-D includes two detailed reports that identify and review the published peer-reviewed epidemiology literature for 2, 4-D. The reports are well described and highlight the strengths and limitations of the body of human literature. As stated in the reports, the "assessment of study quality followed the Office of Pesticide Programs (OPP) epidemiology framework" (as publicly posted in 2016)." Included in the 2, 4-D reports is the OPP "Framework" quality template (Table 2. Summary of study quality considerations), which provides a rubric to evaluate study parameters of design, exposure assessment, outcome assessment, confounder control statistical analysis and other bias. The EPA Tier II cancer and non-cancer reports include a summary of each publication assessed as part of the 2, 4D Registration Review, following this template in each report's Appendix "B".

The 2, 4-D RHHRA is one of the first to utilize the 2016 OPP "Framework." Given that EPA is using the approach in its weight of evidence for regulatory decision making, CLA will provide several recommendations based on its observation of the epidemiologic reviews. While the CLA recommendations are not in opposition to the OPP conclusions regarding the current RHHRA, we believe it essential that the recommendations be considered to bolster the scientific integrity and transparency of this and future reviews.

1. Identify and label the quality conclusion (High, Moderate, Low) for each parameter in the studies reported in the following tables. The "Framework" clearly defines study design. However, other parameters are descriptive, and the quality components fall on a continuum and do not appear to be dependably concluded. A transparent designation for each parameter mirrors other quality instruments (OHAT 2015, LaKind et al. 2014).

2. Obtain consistency with conclusions. Numerous publications represent a single subject cohort [i.e. the Agricultural Health Study (AHS)].

When exposure assessments and outcome assessments are identical, the quality description and designation also should be identical. When methods are similar across studies, the descriptions and designations can be compared. As an example, different studies using the same self-administered questionnaires as data should not have different quality assessments; the quality would be identical as the data is identical. One study should not administer a quality conclusion of higher or lower for exposure and outcome if identical data is being utilized for identification of research questions.

3. Clearly identify and determine the impact of the risk estimate due to "other bias." Listing the biases of recall and exposure misclassification, and lack of gender diversity, for example, aids in overall understanding of study design, but is not informative given that so many studies share these limitations. The limitations of the biases should be discussed in greater detail and complexity.

4. Inclusion of dose-response as an additional study evaluation parameter. Dose-response analysis is important to causal inference in evaluating epidemiology studies. It brings together exposure assessment and the fitness and relevance of the statistical analyses. The tool of dose-response allows these non-mutually exclusive factors to visibly provide explanation of risk. The quality of both (exposure and statistical analyses) can be high but a given publication may not include any dose-responses analyses. If the data are collected but not reported, the absence of a dose-exposure relationship can be a topic for discussion with the study investigators as a part of a Tier III analyses.

   Including dose-response as a unique quality will enhance both the transparency and consistency of the epidemiology quality reviews. The 2, 4-D RHHRA recognized the following:

Studies that characterized the exposure-response relationship (e.g. with a dose-response curve or trend statistic) were, in general, considered higher quality in EPA's evaluation of studies than studies that did not characterize exposure-response. (page 8).

[3] Office of Health Assessment and Translation, OHAT. 2015. Handbook for conducting a literature-based health assessment using OHAT approach for systematic review and evidence integration. edited by Division of the National Toxicology Program.

[4] LaKind, J. S., J. R. Sobus, M. Goodman, D. B. Barr, P. Fürst, R. J. Albertini, T. E. Arbuckle, G. Schoeters, Y. M. Tan, J. Teeguarden, R. Tornero-Velez, and C. P. Weisel. 2014. "A proposal for assessing study quality: Biomonitoring, Environmental Epidemiology, and Short-lived Chemicals (BEES-C) instrument." *Environ Int* 73:195-207. doi: 10.1016/j.envint.2014.07.01

Tables 1-4 Provide perspectives based on recommended changes to study classifications by CLA - recommendations with direct examples from the Tier II Carcinogenic Effects Summary, and CLA provides a suggested administration of the recommendations. Below each table are brief descriptions of recommendations as they related to the example.

Table 1. Example from EPA's Cancer Review Summary of Articles Selected for Inclusion

Journal Article	Study Design	Exposure Assessment	Outcome Assessment	Confounder Control	Statistical Analyses	Risk of (other) Bias
Actual perspective provided by study authors for design and study parameters						
Andreotti, G., et al., 2009	Prospective cohort study White males only	Self-administered questionnaire to obtain detailed information on farm activities and use of pesticides at enrollment and take home	State cancer and death registries	Moderate control for confounders. Controlled for age, smoking, diabetes, and applicator type	Unconditional logistic regression to obtain OR and 95% CI; a small number of exposure cases ($n \leq 17$)	Small number of exposed cases, could not test for statistical interaction due to small number of cases, lack of racial and gender diversity.
Suggested perspectives to ascribe study quality to each study parameter						
Andreotti, G., et al., 2009	High (1) Prospective cohort study (AHS) (2)	High Self-administered at enrollment and take home (3)	High State cancer and death registries	Moderate Moderate control for confounders. Controlled for age, smoking, diabetes, and applicator type	Moderate Unconditional logistic regression to obtain OR and 95% CI; a small number of exposure cases ($n \leq 17$) (4)	(5)

1. **Transparency**. Provide the quality determination (High, Moderate, Low) for each parameter.
2.
    a. **Correction.** The AHS applicators do include some women, and men of other races.
    b. **Consistency.** Label the studies that are from the same underlying data and/or data collection. Examples include the AHS, DOW retrospective cohort study, the six province Canada study, Iowa case-control study, UFW study. The quality of the exposure and outcomes should be identical. The confounding control and statistical analyses may vary for each publication.
3. **Consistency**. Establish the quality determination of the AHS enrollment and take-home questionnaires. This can be applied for all AHS publications that rely on these questionnaires. Notably, the AHS is an occupational cohort for which the reliability of responses may be better than for population-based studies.
4. **Correction.** The number of exposed cases is incorrect. There were 48 exposed cases (spouses and applicators). There were sufficient numbers to evaluate never used ($n = 17$), < 370 ($n = 17$) and > 370 intensity weighted ($n = 24$) among the applicators.
5. Diversity and sample size are relevant in other parameters, but not consistently addressed.

Table 2. Example from EPA's Cancer Review Summary of Articles Selected for Inclusion

Journal Article	Study Design	Exposure Assessment	Outcome Assessment	Confounder Control	Statistical Analyses	Risk of (other) Bias
Actual perspective provided by study authors for design and study parameters						
Cantor et al., 1992	Case-control study	Questionnaire answered by subjects or proxy for deceased subjects	State registry or special surveillance program with histopathological verification	Moderate adjustment. 2,4-D risk estimate not adjusted for other pesticides. Adjustment for vital status, age, state, smoking, family history of lympho-poietic cancer, non-farming job related to NHL in the study, exposure to hair dyes, exposure to other substance associated with NHL in the study. Males only	Appropriate. Unconditional logistic regression to obtain ORs and 95% CIs	Acknowledge other sources of bias. Recall bias, willingness to participate may be related to farm residence or occupation as farmer, use of proxy for deceased, exposure misclassification.
Suggested perspectives to ascribe study quality to each study parameter						
Cantor et al., 1992	Moderate Case-control study Males only	Moderate to low Self-reported questionnaire (30% were proxy respondents) (1)	High State registry or special surveillance program with histopathological verification	Moderate 2,4-D risk estimate not adjusted for other pesticides. Adjustment for vital status, age, state, smoking, family history of lympho-poietic cancer, non-farming job related to NHL in the study, exposure to hair dyes, exposure to other substance associated with NHL in the study.	Moderate. Unconditional logistic regression to obtain ORs and 95% CIs	Low (quality) The high number of proxy respondents may have biased the results. The authors did not provide results stratified by type of respondents.

1. Quality. The percentage of proxy respondents is relevant. This can be discussed further in the risk of bias. Notably, Zahm et al., 1990 report very different results when stratified by type of respondents.

Table 3. Example from EPA's Cancer Review Summary of Articles Selected for Inclusion.

Journal Article	Study Design	Exposure Assessment	Outcome Assessment	Confounder Control	Statistical Analyses	Risk of (other) Bias
Actual perspective provided by study authors for design and study parameters						
Mills and Yang, 2005a	Nested case-control study	Written pesticide usage reports and online summaries	State cancer registry files	Moderate adjustment. Adjusted for age, duration of union affiliation, socioeconomic level, fertility, and date of first union affiliation	Unconditional logistic regression to obtain OR and 95% CI	Ecologic nature of exposure assessment
Mills and Yang, 2007		Three different types of records/databases: UFW records (occupational history), grower's contracts to establish the crop/commodity the member was exposed to, and the California Department of Pesticide Regulation (specific pesticide usage)	State cancer registry files	Adjusted for sex	Mantel-Haenszel method and an unconditional logistic regression to obtain OR and 95% CI	Recall bias, exposure misclassification, lack of control for confounders
Suggested perspectives to ascribe study quality to each study parameter						
Mills and Yang, 2005a	Moderate Nested case-control study (UFW) (1)	Low Three different types of records/databases: UFW records (occupational history), grower's contracts to establish the crop/commodity, and the California Department of Pesticide Regulation (specific pesticide usage) (2)	High State cancer registry files	Moderate Adjusted for age, duration of union affiliation, socioeconomic level, fertility, and date of first union affiliation	Moderate Mantel-Haenszel method and an unconditional logistic regression to obtain OR and 95% CI. Dose analyses by no use, low and high. (3)	Low Ecologic nature of exposure assessment without validation of exposure to participants or evaluation of direction of misclassification bias.

Mills and Yang, 2007	Nested case-control study (UFW) (1)	Low Three different types of records/databases: UFW records (occupational history), grower's contracts to establish the crop/commodity, and the California Department of Pesticide Regulation (specific pesticide usage) (2)	High State cancer registry files	Moderate Adjusted for age, sex, length of union affiliation, date of first union affiliation, duration of union membership	Moderate Mantel-Haenszel method and an unconditional logistic regression to obtain OR and 95% CI. Dose analyses (#lb; 4 lev)	Low Ecologic nature of exposure assessment without validation of exposure to participants or evaluation of direction of misclassification bias

1. **Consistency.** By labeling the study, the same exposure and outcome assessments can be used.
2. **Transparency**. Provide the quality determination (High, Moderate, Low) for each parameter. Although three types of records were used to establish exposure, there was no confirmation that the individual was working in the treated field AFTER the treatment.
3. **Quality.** The three Mills et al. publications each used different categorizations for exposure [Low vs. High; None/Low/High, and four (4) levels by pounds]. Consider adding dose-response as a new parameter

Table 4. Example from EPA's Cancer Review Summary of Articles Selected for Inclusion

Journal Article	Study Design	Exposure Assessment	Outcome Assessment	Confounder Control	Statistical Analyses	Risk of (other) Bias
Actual perspective provided by study authors for design and study parameters						
Beard et al., 2013	Case-control study	Self-administered questionnaire at enrollment for spouses of enrolled applicators obtaining farm exposure, general health information, and reproductive health history	Self-reported responses by cases during follow-up telephone interview	Adjusted for education level, age at enrollment, ever diagnosed with diabetes, state of residence, and drop out, as well as account for number of study subjects who did not complete the follow-up interview	Log-binomial regression to obtain RR and 95% CI	Self-reported case ascertainment could have led to misclassification; lack of exposure data (frequency and duration) could have caused exposure misclassification.
Beard et al., 2014	Case-control study Males only	Two self-administered questionnaires at enrollment and follow-up regarding past pesticide exposure	Cases were ascertained by physicians	Adjusted for confounders including age, diabetes diagnosis, education level, and state or residence, as well as missing covariate data and study drop-outs	Polytomous logistic regression was used to obtain OR and 95% CI	Exposure misclassification from self-reported exposures

Suggested perspectives to ascribe study quality to each study parameter						
Beard et al., 2013	High Prospective cohort study (AHS) Women only (1)	Moderate Self-administered questionnaire at enrollment for spouses of enrolled applicators (2)	Moderate Self-reported responses (3)	High Adjusted for education level, age at enrollment, ever diagnosed with diabetes, state of residence, and drop out, as well as account for number of study subjects who did not complete the follow-up interview	Moderate Log-binomial regression to obtain RR and 95% CI, no dose response analyses (4)	Moderate Self-reported case ascertainment could have led to misclassification; lack of exposure data (frequency and duration) could have caused exposure misclassification.
Beard et al., 2014	Moderate Nested Case-control study (AHS) Males only (1)	High Two self-administered questionnaires at enrollment and follow-up regarding past pesticide exposure (2)	Moderate Self-reported responses (3)	High Adjusted for confounders including age, diabetes diagnosis, education level, and state or residence, as well as missing covariate data and study drop-outs	Moderate Polytomous logistic regression was used to obtain OR and 95% CI, No dose-response analyses (4)	Moderate Exposure misclassification from self-reported exposures

1. **Consistency.** The AHS is not a typical case-control study. The design can be shown either as a prospective cohort study or as a nested-case control study, based upon the analysis. In general, if providing information on gender, it also should be provided for the studies limited to women.
2. **Transparency**. The exposure assessment of the AHS can be considered high quality because of the reliability studies of the questionnaire. However, these are limited to the applicators. As an occupational study, the applicators logically are more knowledgeable about the products they use. Is this also true of their spouses?
3. **Correction.** The studies of depression by Beard et al. (2013 and 2014) were not based on cases ascertained by physicians. The AHS participants self-reported that a doctor had diagnosed them.
4. Neither publication incorporated a dose-response in their analyses.

Concluding Remarks

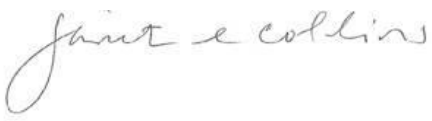
CLA acknowledges the EPA approach to include and evaluate the body of human epidemiology data for Human Health Risk Assessments, with reservations that need to be addressed for transparency and consistency in decision making. The 2016 Office of Pesticide Programs "Framework" is not presently considered a regulatory requirement but rather a guideline. Guidelines such as Good Laboratory Practices are valuable for investigators, stakeholders and reviewers to conduct and require the highest quality data possible. An open and transparent process for epidemiologists to use in proposed and published research will benefit all stakeholders, and enhance the usefulness of the outcomes from those studies.

We continue to welcome the opportunity to work with EPA and other federal agencies in pursuit of scientifically balanced approaches to human health risk assessment.

Should you have any questions or wish to discuss these issues further, please contact me directly by email (jcollins@croplifeamerica.org) or directly (+1-202-833-4474).

Thank you for your consideration of these comments.

Respectfully,



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