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Via Federal eRulemaking Portal
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Mr. Joel Wolf
OPP Docket
Environmental Protection Agency
Docket Center (EPA/DC), (28221T)
1200 Pennsylvania Ave., NW
Washington, DC 20460–0001

Re: Chlorpyrifos Registration Review; Revised Human Health Risk Assessment
Docket ID: EPA-HQ-OPP-2008-0850

Mr. Wolf:

CropLife America (CLA) submits these comments in response to the revised human health risk assessment (HHRA) for the registration review of chlorpyrifos (CPF) by the U.S. Environmental Protection Agency (EPA or the Agency) announced on January 14, 2015. 80 Fed. Reg. 1909; 80 Fed. Reg. 13371 (March 13, 2015) (extending comment period). CLA 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 U.S. Our member companies produce, sell and distribute virtually all of the crop protection technology products, including CPF, used by American farmers. CLA members support the scientific, risk assessment based regulation of their products. CLA regularly comments on issues of regulatory significance to CLA member companies and the broader agricultural community.

CLA appreciates the opportunity to provide comment on the CPF HHRA conducted by the Agency. This HHRA has the potential to establish precedents that could impact the HHRA process for other pesticide active ingredients relating to EPA's review processes and policies, particularly, how and what data is considered with respect to regulatory decision making. CLA's comments focus on: (i) the use of pharmacokinetic (PBPK) modeling to data derived extrapolation and treatment of uncertainty, (ii) the use of epidemiology studies, and (iii) the drinking water estimates used to determine the ongoing use of CPF on agronomic crops.

With respect to the CPF HHRA, the Agency has reviewed data for one of the mostly widely tested pesticide active ingredients. The global CPF toxicological database is extensive, and the effects and endpoints are well defined. Incorporating this information into a HHRA is no small task and the Agency has taken its usual comprehensive and

thorough approach to conducting this review, with a couple of exceptions with which CLA has considerable concern.

CLA commends the Agency for successfully incorporating recent, cutting edge science into its review process to enable better understanding of the interspecies relationships, using data derived extrapolation factors (DDEF) developed through the use of PBPK modeling. This has allowed the Agency to conclude that the uncertainty of extrapolating data from rodent studies to effects in humans no longer warrants the 10x interspecies Uncertainty Factor (UF). In other words, rodents are an appropriate model for the effects of CPF in humans, and the interspecies UF can be reduced to 1x. It has also enabled the Agency to move to a 4x uncertainty factor when considering different population subgroups, with the exception of pregnant women which retains the 10x UF.

The significance of this methodological approach extends to compounds other than CPF. It is a welcome development that reflects EPA's use of the best science available, and moves away from default values which are designed to address data gaps in a highly conservative manner. The use of DDEF to demonstrate the extent to which rodent studies provide human relevant data is a significant development for pesticide compound reviews since the Agency is precluded from conducting human trials. We encourage the Agency to continue to incorporate PBPK modeling in this and future assessments. We also encourage the Agency to consider the most recent work on PBPK modeling for pregnancy, which was not included in this review.

Yet CLA has serious concerns regarding the use of epidemiology studies for human health risk assessment and the Agency's estimates of drinking water exposure, which do not reflect data provided by the registrant, the extensive monitoring data available for CPF, or actual use patterns but rather are derived using conservative modeling data.

Role of Epidemiology Studies within the HHRA:

EPA Office of Pesticide Program (OPP)'s Draft Framework for Incorporating Human Epidemiologic and Incident Data in Health Risk Assessment (January 7 2010) references "a weight of evidence analysis for evaluating epidemiology and human incident data, such that all available data are evaluated and conclusions made on the preponderance of information rather than relying on any one study" that "OPP will use the best available data across multiple lines of evidence" and "use modified Bradford Hill criteria like those in the Mode of Action framework as a tool for organizing and integrating information from different sources". EPA-HQ-OPP-2009-0851-0004 at p.27. These statements should be kept in mind when reading the comments below.

The Agency's incorporation and consideration of epidemiologic studies in the HHRA is of relevance to risk assessments going forward because in the case of the CPF review the specific selection of epidemiology studies is narrow, and omits other relevant

studies without explanation; the weighting given to those studies relative to the totality of the data, particularly the 40 CFR §158 toxicological data, lacks scientific justification; and the availability of raw data from these studies, or rather the lack thereof, is not consistent with the data provision requirements or processes used to consider data provided by the registrant.

The Agency identified only three epidemiological studies for incorporation into the risk assessment. Yet multiple reviews have looked across a far greater number of epidemiology studies and publications and concluded that at the measured levels of exposure, the evidence from these studies is insufficient to show causality between CPF and adverse neurodevelopment effects in infants and children (Burns et al. 2013; Eaton et al. 2008; Li et al. 2012a; Li et al. 2012b; Mink et al. 2012). It should be noted that university researchers (Ntzani et al. 2013), under contract from the EU's European Food Safety Authority (EFSA), reviewed 603 epidemiology studies presenting over 6000 analyses published since 2006 and concluded there is no evidence to suggest an association between pesticide exposure, including CPF, and neurodevelopmental effects. In a separate publication, EFSA (2014) also concluded the epidemiology data are not sufficiently robust to support a causal relationship with neurodevelopment effects.

It is critically important that exposures cited in epidemiologic studies be evaluated against exposures and internal doses used in toxicological studies when assessing environmental exposures to compound and the potential to cause harm. This is particularly important for human health conditions that are influenced by a multiplicity of factors including lifestyle. Apical endpoints such as IQ decrements, are classic examples of conditions impacted by far more than exposure to any one or any one class of substances.

The Columbia Study provided estimated exposures which were 5000 times lower than the threshold of 1mg/kg bw/day used as the threshold level for CPF exposure by the EPA. The EPA threshold dose was derived from extensive animal testing where neurodevelopmental and behavioral effects were only reported at CPF doses higher than 1mg/kg bw/day. EPA provides no evidence as to why it would diverge from its previous threshold levels for exposure when those thresholds have been derived through extensive toxicological testing.

While the Agency cites two other epidemiology studies (Mt Sinai and CHAMACOS) as supporting the findings of the Columbia Study, these studies are confounded by the way in which exposure was characterized through the use of urinary metabolites, as they may arise as much from consumption of the metabolite itself – which is harmless – as from the parent compound CPF. A recent study (Reiss, 2014) (in press) reviewed 14 epidemiological studies, including the studies referenced in the EPA Risk Assessment, and examined the effect of low-level exposures to organophosphorus (OP) insecticides

in non-occupations populations and concluded that the available evidence from these studies does not establish that low level exposures to OP insecticides cause adverse birth outcomes or neurodevelopmental problems in humans.

The introduction and consideration of epidemiologic studies in the HHRA had a strong influence on the Agency's regulatory decision making for CPF, and caused EPA to reset the Food Quality Protection Act (FQPA) safety factor to 10X, from its previous level of 1x. This is despite the fact that the exposures were orders of magnitude lower than the threshold dose established through *in vivo* toxicological testing in animals, and that EPA in this HHRA demonstrates that the doses used and effects seen in those animal studies are equivalent to the responses that would be seen in humans at equivalent doses. The revision of the FQPA safety factor (SF) back to 10x has a profound impact on the calculation of the "risk cup" and the number of permitted uses of a compound. This FQPA factor was also interpreted into the calculation of occupational exposures. The latter is a fundamental policy shift by the Agency and that this was done without appropriate scientific and public scrutiny is of considerable concern to our members. It also suggests that the epidemiology study conclusions, instead of being evaluated within the context of the extensive toxicological data, were taken as a standalone indicator of harm that drove the risk assessment and resulting regulatory decision making on CPF.

CLA members provide extensive scientific data in support of registration submissions, and the Agency imposes rigorous requirements on study conduct and evaluation of these data. Data from non-guideline studies, including human, animal, and *in vitro*, considered in the risk assessment also meet rigorous standards for inclusion. Epidemiologic studies included in an Agency regulatory decision should also be required to meet the standards required for studies specified in 40 CFR §158. Specifically, studies should be conducted according to the Good Laboratory Practices (GLP) standard which requires all raw data be made available to the Agency for review and analysis. Since risk quotients derived from an epidemiologic study are highly dependent on which data are included, and how it is segregated prior to analysis, the analysis must be open to the Agency's verification using the raw data. When no raw data are available for assessment purposes, it is not possible for the Agency to verify the outcomes or conclusions of such studies. Yet even though it is critical that conclusions drawn from epidemiologic studies be cross checked against findings from mechanistic studies and toxicology data, it is not clear in the case of this review how the toxicological study conclusions could have been cross checked against those of epidemiologic studies wherein no primary data are available.

All data sources used for regulatory decision making should be made available to the Agency, so as to ensure appropriate statistical assessment and comparators. The lack of transparency and data reliability inherent in the lack of raw data for Agency review in

the HHRA is an overarching concern with regard to how conclusions for regulatory decisionmaking are drawn for all crop protection compounds.

It is also critically important that the exposures cited in epidemiology studies be evaluated against exposures and internal doses in toxicological and mechanistic studies to determine whether or not the environmental exposures to the compound are sufficient to cause harm. According to the EPA 2010 Framework document, consideration of mode of action for the adverse effect – derived from toxicological and mechanistic studies – is considered necessary to the Agency's consideration of epidemiologic studies. However, yet the Agency states that in this case, there is no known mode of action for these effects. Where modes of action do exist, then the issue of exposure and dose become critical to parsing out the drivers of the disease, and the consideration of confounding factors must be rigorous and comprehensive.

On behalf of CLA members, we ask the Agency to ensure: (i) it has access to the raw data from epidemiologic studies used for regulatory decisionmaking; (ii) specific acceptance and exclusion criteria for studies used in the regulatory decision making are clearly articulated; (iii) the best available information is considered, including studies for which no effects or negative effects are reported; (iv) a comparison of the human exposure potential from epidemiologic studies is made against points of departure (POD) from toxicological studies; and (v) a determination is made as to whether the exposures presented in the studies were sufficient to cause negative human health effects.

Should the Agency consider use of epidemiologic studies in future HHRH risk assessments, the findings from those studies should be put into appropriate context against the relevant guideline toxicological studies (40 CFR §158), that produce fundamental, replicable data required by the Agency for registration of crop protection product compounds.

The Agency's estimates of drinking water exposure.

The drinking water exposure assessment conducted by EPA could set a precedent for the regulatory review of other compounds. The accuracy of the models and assumptions used to derive the exposure estimates must be known, particularly with respect to the environmental monitoring data presented by each registrant. Monitoring data collected and reported as part of the registration package are particularly relevant in the assessment of a specific compound. There is also considerable monitoring data available as a result of government monitoring activities (for example the US Geological Survey data), which have utility and should be considered. As new models for drinking water exposure are developed, some comparison with outcomes from the use of specific monitoring data is essential.

Drinking water exposure is used by the Agency in its calculations of aggregate exposure. In many cases, the Agency relies on conservative modeling estimates which assume maximum application concentrations and frequencies to derive estimates of exposure. Refinement would be possible with the use of monitoring data, either to the model inputs or using the monitoring data itself to more realistically estimate exposure. In addition to monitoring data, there exists data on pesticide application rates and frequency and this could also be used to refine the extremely conservative use assumptions employed by the Agency. In the case of CPF, the nearly 47,000 monitoring data points, and the data on actual application rates and product use were not used to refine the model inputs, and, in fact, the model estimated drinking water exposures based on a worse-case scenario.

Our members have long expressed concern over the Agency's assumption of peak exposures when modeling drinking water assessments. Two studies submitted to EPA, but not considered here, would have informed the Agency with respect to its consideration of the monitoring data and with respect to the toxicological impact of the CPF metabolite in drinking water. The Agency should have considered these two studies in its EDWA in order to meet the requirement to use the "best available science".

In particular, the first study provided an in-depth analysis of the monitoring data. This study is of particular relevance to our members as it provides the Agency with methodology on how to integrate monitoring data into modeling to advance the approach and move to more realistic assessments. It should be noted that when the highest monitoring concentrations for CPF were factored into the various crop use scenarios currently permitted by the Agency, all uses passed, thus even at the highest concentrations in drinking water, the aggregate exposure for all uses was acceptable.

Another concern is that when the Agency compared the model output to the monitoring data, it concluded that the EDWCs are "within one order of magnitude of the measured concentrations reported in the monitoring data" and that these assumptions "do not appear to lead to an overly conservative estimate of exposure" (Page 89 of the CPF HHRA). Yet when the modeling data were used, contrary to when the monitoring data were applied, most use scenarios failed. This speaks to an excessively conservative estimate of exposure and the inappropriate assumption that an "order of magnitude" difference between the mode predictions and monitoring is an acceptable standard for model performance. Our members' experience speaks to acceptable model performance within the range of a 3x-4x difference, not 10x. The acceptance of a 10x difference between modelled and monitored exposures therefore effectively results in an additional 10x uncertainty factor being applied to the reference dose, on top of the UF already considered when evaluating the toxicological data. Furthermore, the stated acceptable level of model performance of one order of magnitude is not associated with any written definition of regulatory objectives; the use of such an accuracy measure

should be properly assessed through the usual, transparent scientific and public comment process if this is intended to represent Agency policy for future assessments.

The approaches and potential policies or standards of evidence that could be set by use of such models for assessment of exposure, as used in the chlorpyrifos assessment, have potential implications for the HHRA of all crop protection chemicals submitted to the Agency for regulatory decisionmaking. We are concerned that use of modeling data which are not rationalized against specific monitoring data will result in overly conservative outcomes from the calculations. Therefore, we strongly believe that it is imperative to rationalize the model used when overlaid with actual monitoring data; short of that, monitoring data (actual on-site data) serve to demonstrate most accurately the state of exposure, and should be the data upon which a regulatory decision can be made. Should the Agency use such exposure estimates and models *in lieu of* actual monitoring data when developing the regulatory decision, some stakeholder consultation, external scientific input, and prior written guidance is essential to ensure adequacy and relevance of data needed to make a regulatory decision.

The approaches, potential policies, or standards that could be set by what has been done in this assessment could potentially impact the continued availability of all crop protection tools for growers. Growers need a diverse portfolio of products to manage their crop protection needs, and to combat resistance in pest species. CLA supports the availability of a broad portfolio of products necessary for crop protection, pest control, and to combat the development of pest resistance; we support the comments submitted by growers which speak to the importance of CPF as one of the range of necessary components to the larger agronomic toolkit required by growers. Crop protection products also provide benefits to society as whole by enabling a predictable supply of safe, nutritious and affordable food. HHRA should not be so conservative or removed from actual agricultural practices as to present an unrealistic overestimate of risk and thereby prevent the availability of a valuable crop protection products which can be used safely and beneficially.

As an example, we reference the comments provided to the Agency by the National Association of Agricultural Aviators and Schertz Aerial Service, Inc. These comments address the determination by EPA that certain occupational risks to ground crews involved in the aerial application of CPF are not capable of adequate mitigation with additional Personal Protective Equipment (PPE) or engineering controls to render them safe. If EPA concludes the risks cannot be mitigated, then this further restricts the use of these important products. However, and not unlike the determination of aggregate exposure, this determination is also based on the interpretation of the epidemiological studies within the HHRA, the use of an overly conservative FQPA SF coupled with inappropriate exposure assumptions. It also ignores existing publications and studies which could provide improved and more refined exposure estimates (cited in the NAA and Schertz comments).

In summary, CLA appreciates the opportunity to provide comments on this important document as it signals some change in the Agency approach to regulatory decision making in developing human health risk assessments.

We request the Agency consider the impact of the current approach to drinking water modeling on this and future HHRA, as it adds additional layers of conservatism to the existing Uncertainty Factors and Safety Factors calculated into the reference dose. In this particular case, the effect of the added 'precaution' in the assessment, to increase the FQPA SF from 1x to 10x, coupled with the 10x factor imposed by the estimated drinking water exposure model further is to significantly reduce the allowable crop uses and constrain the consideration of risk mitigation approaches for occupational exposures.

We request the Agency ensure that primary data are available if those studies are included in an assessment and that when using models for assessing exposure, conservative assumptions are not included when the data do not support the need for such precaution. We are concerned over the lack of transparency inherent in accepting studies for which no raw data are available. We are concerned over excessively conservative drinking water exposure modeling which does not connect with the UF and SF already factored into the reference dose. We are concerned that this potentially precedent-setting HHRA could impact not only CPF but other member compounds going through registration review. We request the Agency to address these concerns.

We welcome the opportunity to discuss these issues more fully as the Agency further develops the regulatory decisionmaking approaches for human health risk assessment for crop protection products. Should EPA require specific data from CropLife America, please contact us directly at CThorp@croplifeamerica.org or (202) 872-3866.

Regards,

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