United States Department of Agriculture

January 17, 2017

Jack E. Housenger, Director
Office of Pesticide Programs (7501P)
U.S. Environmental Protection Agency
1200 Pennsylvania Avenue NW
Washington, DC 20460

Dear Mr. Housenger,

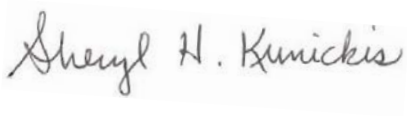
USDA appreciates the opportunity to comment on EPA's proposal to revoke chlorpyrifos tolerances, and in particular the new underlying risk assessment that was announced on November 17, 2016 ("Chlorpyrifos; Tolerance Revocations; Notice of Data Availability and Request for Comment," 81 FR 81049, Docket ID EPA-HQ-OPP-2015-0653). As you know, EPA is proposing this action in response to a petition to revoke chlorpyrifos tolerances submitted by the Natural Resources Defense Council and Pesticide Action Network North America in 2007.

USDA has both grave concerns about the EPA process that has led to the Agency publishing three wildly different human health risk assessments for chlorpyrifos within two years, and severe doubts about the validity of the scientific conclusions underpinning EPA's latest chlorpyrifos risk assessment. Even though use of the Columbia Center for Children's Environmental Health (CCCEH) study to derive a point of departure was criticized by the FIFRA Scientific Advisory Panel, EPA continues to rely on this study and has now paired it with an inadequate dose reconstruction approach.

In light of these developments, USDA calls on EPA to deny the NRDC/PANNA petition to revoke chlorpyrifos tolerances. This would allow EPA to ensure the validity of its scientific approach as part of the ongoing registration review process, without the excessive pressure caused by arbitrary, litigation-related deadlines.

Our detailed comments on the latest chlorpyrifos risk assessment follow. We look forward to continuing to work with EPA to ensure that pesticides remain both safe to the public and available to U.S. farmers. Please do not hesitate to contact me if you have any further questions.

Sincerely,



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January 17, 2017

USDA Comments on the Risk Assessment Underlying the Reopened Proposed Rule "Chlorpyrifos; Tolerance Revocations; Notice of Data Availability and Request for Comment" (Docket ID EPA-HQ-OPP-2015-0653)

Science is the backbone of the EPA's decision-making. The Agency's ability to pursue its mission to protect human health and the environment depends upon the integrity of the science on which it relies. The environmental policies, decisions, guidance, and regulations that impact the lives of all Americans every day must be grounded, at a most fundamental level, in sound, high quality science.

– Excerpt from *Scientific Integrity Policy*, U.S. Environmental Protection Agency

Introduction

The "Revised Human Health Risk Assessment for Registration Review" dated November 3, 2016, is the third human health risk assessment for chlorpyrifos that EPA has released, and that USDA has reviewed and commented on, within the past two years. Typically, three risk assessments for the same hazard published so close together represent successive attempts at improvement and refinement, with the goal of reducing uncertainty and improving the reliability of the results. However, EPA's three risk assessments resemble more of a scattershot approach, with the agency switching between different health outcomes and points of departure, and adopting widely varying dose measurement and reconstruction approaches.

In its latest assessment, EPA has stopped using the dose data from the Columbia Center for Children's Environmental Health (CCCEH) study it had endorsed in its previous risk assessment just eight months earlier, and instead has chosen to rely on a dose-reconstruction approach to identify a point of departure. This dose reconstruction approach supposedly estimates the amount of chlorpyrifos to which women in the CCCEH cohort might have been exposed in their homes around the turn of the century. It is not based on any empirical data, but rather on conversations EPA had with "several" pesticide applicators in 2016 in which they "recalled" what the "predominant" use of chlorpyrifos "in New York City apartment buildings" was 15-20 years earlier. Without any actual data as to use of chlorpyrifos in the cohort members' apartment buildings, let alone their individual apartments, EPA is merely *guessing* that the women in the CCCEH cohort were exposed to one crack-and-crevice application of chlorpyrifos per month.

These exposure guesses are then linked to adverse health outcomes that EPA's own Scientific Advisory Panel (SAP) has questioned as being either statistical artifacts or not caused by chlorpyrifos exposure. In addition, the latest risk assessment is still based on just the single, not replicated, and unconfirmed CCCEH study. Many weaknesses inherent in the study have been identified by the SAP and others, which undermine its suitability for determining a point of departure. These weaknesses remain unaddressed in EPA's latest risk assessment. This cannot be the type of "sound, high quality science" the writers of EPA's Scientific Integrity Policy envisioned as the "backbone of the EPA's decision-making." USDA has grave concerns that ambiguous response data from a single, inconclusive study are being combined with a mere *guess* as to dose levels, and the result is being used to underpin a regulatory decision about a pesticide chemical that is vital to U.S. agriculture, and whose removal from market would have a major economic impact on growers and consumers.

Our more detailed comments follow, and are divided into two sections, substantive and procedural. USDA requests a response that addresses our comments both comprehensively, and on a paragraph-by-paragraph basis.

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Substantive Concerns

Over the past two years, USDA has observed EPA's chlorpyrifos risk assessments transition from a more traditional, incremental approach based on combining a point of departure from a well-established health outcome (10 % red blood cell acetylcholinesterase inhibition, or 10 % RBC AChEI) with retention of a 10X FQPA safety factor based on some new epidemiological observations, to a completely novel, even radical, approach of basing the entire risk assessment, and through it the regulatory and economic future of this major agricultural chemical, on a single limited and problematic epidemiological study.

Throughout the latest risk assessment and the accompanying notice in the Federal Register, EPA gives the impression that the Agency has addressed concerns voiced by the April 2016 SAP and is following the SAP's recommendations. For example, in the Federal Register Notice published on November 17, 2016, which announced the availability of the latest risk assessment, EPA claimed that it "modif[ied] the methods and risk assessment . . . in accordance with the advice of the SAP" (81 FR 81050). The SAP exists to provide independent scientific advice to the Agency; as such the SAP's findings are particularly important when they disagree with an approach taken by EPA. Even though SAP reports are not legally binding on the Agency, USDA strongly encourages EPA to thoroughly consider the advice received from the SAP. An objective, comprehensive review of the meeting minutes of the SAP's April meeting, published July 20, 2016, simply does not lead to the conclusion that SAP concerns have been addressed. Instead, the latest risk assessment raises additional and more acute concerns about the viability of EPA's risk assessment approach and the reliability of its findings.

EPA's latest risk assessment rests on three central conclusions. USDA disagrees with all three.

1. **EPA concludes that studies show an actual effect on working memory among children in the CCCEH cohort**

In order for a study to be meaningful for deriving a point of departure, it must detect an actual health effect. EPA has chosen a 2 % change in working memory, measured at age 7 and discussed in the Rauh et al. (2011) study of the CCCEH cohort, as the critical effect for its last two risk assessments, the first of which was reviewed by the SAP in April. There was considerable disagreement among SAP members as to whether this 2 % change is even significant or anything more than a statistical artifact:

- "The [SAP] was conflicted with respect to the importance of a 2% change in working memory."
- "Some members considered a 2% change in working memory (less than one standard deviation in the distribution of scores in the general population) to be of questionable biological significance."
- "By definition, the [standard deviation] for an essentially unexposed population is really 15%. A 2% reduction seems to be a particularly low threshold for concluding 'abnormal.'"

Quotes from FIFRA SAP meeting minutes on chlorpyrifos (July 20, 2016)

If the Rauh et al. study failed to detect a true health effect, any further discussion on the use of this study to derive a point of departure would be moot. USDA does not deny that some SAP members did argue that a 2% change in working memory is a significant health effect. Rather than taking a position as to whether the observed 2 % decrement in working memory is "real" or "significant," USDA merely wishes to highlight the considerable disagreement within the EPA SAP as to this very basic question. If the experts convened by EPA cannot even agree that a health effect (let alone an *adverse* health effect) was observed, this severely weakens the study's suitability as the sole quantitative foundation of a major, economically significant risk assessment. Equally concerning is EPA's failure to address in its most recent risk assessment the questions raised by the SAP.

2. EPA concludes that the 2 % change in working memory was caused by prenatal exposure to chlorpyrifos

Establishing causality between the exposure of interest (in this case, prenatal chlorpyrifos exposure) and the observed health effect (in this case, a 2 % change in working memory measured at age 7) is a crucial prerequisite to using the CCCEH cohort data in quantitative risk assessment. EPA's latest risk assessment does nothing to address the April 2016 SAP's strongly-worded concerns regarding the lack of established causality. If anything, EPA's Federal Register Notice accompanying the risk assessment further obfuscates the SAP's conclusions. It states that "generally, however, the FIFRA SAP agreed with the overall conclusion of the CCCEH study, i.e. the *association* between prenatal chlorpyrifos exposure and neurodevelopmental outcomes in children" (81 FR 81050; emphasis added). Whether or not chlorpyrifos exposure is *associated* with the change in working memory is not the issue here; an association between chlorpyrifos exposure and change in working memory could be the result of a confounding factor or a multiple comparisons problem, and thus be meaningless for risk assessment.

Rather than association, the relevance of the CCCEH study depends on whether chlorpyrifos *caused* the change in working memory. The SAP emphatically commented on question of causality (emphases added):

- "The assumption that the impaired working memory and lower IQ measures observed [in the CCCEH study] are caused primarily by a single insecticide (chlorpyrifos) and predicted by the blood levels at time of delivery <u>is not supported by the scientific weight of evidence</u>."
- "Some members of the [SAP] were also concerned about the lack of knowledge of the sensitive window(s) of exposure during pregnancy that would lead to neurodevelopmental outcomes. Without accurate knowledge that exposure occurred during a sensitive window, <u>it is impossible to derive causation</u>."
- "Without any evidence in the animal literature or elsewhere of a mechanism of action that could explain how pg/g levels in blood could impair IQ and/or working memory, <u>there does not appear to be biological plausibility</u>. This is a significant uncertainty." (Biological plausibility is a crucial element for establishing causality.)
- "The [SAP] is not aware of any scientific evidence where pg/g levels in the blood would lead to deleterious neurotoxicological effects in a mammalian system. This lack of data could indicate a lack of biological plausibility."

The majority of the SAP members drew the correct logical conclusion from the absence of indicated causality, namely that use of the CCCEH study in a highly impactful risk assessment is "premature and possibly inappropriate." This is a necessary conclusion EPA refuses to draw, by continuing to rely on the CCCEH study in its latest risk assessment. Even more worrisome is EPA's willingness to portray its latest risk assessment as responsive to the SAP concerns, when in reality it is extremely difficult to see how any continued use of the CCCEH study as a basis for a point of departure is consistent with the SAP conclusions. The larger passage from the SAP minutes reads as follows (emphases added):

- "The majority of the [SAP] considers the Agency's use of the results from a single longitudinal study to make a decision with immense ramifications based on the use of cord blood measures of chlorpyrifos as a [point of departure] for risk assessment as <u>premature and possibly inappropriate</u>. The basis for this <u>majority view</u> includes: 1) an inability to either know, or confidently make assumptions about, aspects of exposure patterns, labor and delivery, and blood collection . . . [and] 5) <u>lack of biological plausibility</u> for how low cord blood (low parts per trillion) concentrations of chlorpyrifos can alter working memory and produce neurodevelopmental impairment."

- "Some Panel members stated that the reliance on single cord blood measurements from only one study (i.e. the CCCEH study) as a primary basis for a highly impactful regulatory decision goes against standard practices of science in the field of toxicology and pharmacology."

EPA argues that it addressed SAP concerns about the cord blood data by no longer using them in its latest risk assessment, having replaced them with the dose reconstruction approach. In doing so, EPA misreads the SAP's concerns. While the SAP did criticize EPA for using a single measurement of cord blood, rather than deriving a time-weighted average, the SAP's fundamental disagreement centered on the fact that the risk assessment was based on just a single study with insufficient evidence of causality between exposure and effect. It is not the cord blood data per se that are the problem, and replacing them with a time-weighted average not based on any relevant exposure data does not improve the risk assessment. Rather, it is EPA's "inability to either know, or confidently make assumptions about, aspects of exposure patterns, labor and delivery, and blood collection," as well as the "lack of biological plausibility" that render the CCCEH study unusable. These criticisms are equally valid whether EPA uses the CCCEH cord blood data or a time-weighted average based on the reconstructed dose data.

EPA's reconstructed doses are not based on any additional exposure data collected from the CCCEH cohort, nor do they help overcome the fundamental lack of biological plausibility and thereby causality. In fact, the SAP criticized the use in the risk assessment of not only the dose data (cord blood measurements), but also of the observed outcome data (change in working memory):

- "It was the Panel's conclusion that the Agency provided insufficient justification for using cord blood chlorpyrifos levels and associated neurobehavioral health outcomes to derive a [point of departure]" (emphasis added).

In the end, the fatal flaw of EPA's use of the CCCEH study is that there is insufficient evidence of causality underlying the observed association involving chlorpyrifos. The problems with the chlorpyrifos cord blood data identified by the SAP cannot be isolated from the CCCEH study as a whole. Instead, the entire study, including the cord blood data, is problematic because it fails to indicate a causal relationship between chlorpyrifos and the health effect. Replacing the cord blood data with a different (and arguably inferior) set of reconstructed dose data, as EPA did in its latest risk assessment, does nothing to improve the quality or reliability of the risk assessment, and introduces new and greater uncertainty rather than decreasing it.

The SAP meeting minutes also restated many other concerns about the CCCEH study that have been previously identified by USDA and others, and that continue to be relevant as long as EPA attempts to use the CCCEH study to derive a point of departure. These include the potential presence of numerous confounding factors that further weaken any claim of causality between chlorpyrifos exposure and the change in working memory, the lack of access by EPA or the public to the raw study data, and questions surrounding the analytical methods used to detect the very low (picogram per gram) levels of chlorpyrifos in the cord blood.

- On confounding factors: "In addition to the air sampling study and the cord blood sampling study indicating exposure of the [CCCEH] study cohort to various pesticides, the cohort was additionally exposed to multiple contaminants including PAHs, tobacco smoke, piperonyl butoxide, and phthalates. . . . The fact that the pregnant mothers were exposed to a complex mixture of chemicals, many of which induce deleterious effects on the same neurobehavioral parameters that chlorpyrifos is reported to affect, increases the level of uncertainty for using measurements of chlorpyrifos alone as the basis for the risk assessment . . . . [T]he environment where the exposure occurred contained multiple organophosphate insecticides and multiple carbamate insecticides . . . . Thus, there was the opportunity for the pregnant mothers to be simultaneously exposed to multiple cholinesterase inhibiting chemicals. Following exposure to such a mixture, it would be biologically impossible to separate the independent effects of each

chemical on a neurochemical or behavioral outcome regardless of the statistical model used" (emphasis added).

- On raw data availability: "Finally, some [SAP] members thought the quality of the CCCEH data is hard to assess when raw analytical data have not been made available, and the study has not been reproduced."
- On the analytical method: "A major source of uncertainty for the [SAP] was the lack of verification and replication of the analytical chemistry results that reported very low levels of chlorpyrifos (pg/g). Imputing quantitative values when the concentration of analyte falls below the level of detection (LOD) was a particular concern, especially given that a large fraction of cord blood samples included in the analyses presented with levels below LOD."

3. EPA uses reconstructed dose estimates that are not based on any empirical data or any actual knowledge of the exposure experienced by members of the CCCEH cohort

EPA used its 2012 Residential SOPs, which are typically used to estimate exposure to a pesticide for the general population, to estimate the doses experienced by the CCCEH cohort. Exposure models, such as the Residential SOPs, are designed to produce conservative exposure estimates that are then compared to experimental dose data derived from animal or human studies. In other words, a study typically supplies actual dose values linked to actual response data, which can then be compared to modeled exposure estimates to determine whether a response is expected in the modeled population.

Dose reconstruction is usually based on an internal dose (biomarker) measurement as a starting point and uses reverse dosimetry to arrive at a corresponding external dose. In this case, EPA has no usable internal dose data, and instead is using exposure models to estimate both the doses received by the individuals in the study, as well as the exposure experienced by the general population. The problem is that there is no cause-and-effect link between the dose estimates provided by the exposure model (Residential SOPs) and the change in working memory observed in the CCCEH study. Any exposure model can produce a huge range of exposure estimates due to both population variability and uncertainty. In this case, the uncertainty around any modeled dose estimate is expected to be massive, since EPA has no way of knowing when, how often, and at what levels chlorpyrifos was applied in the CCCEH cohort members' apartments, nor does EPA know the duration and intensity of exposure experienced by study participants post-application. Did they apply chlorpyrifos themselves and did they do so instead of or in addition to professional applications? How long did they spend in the apartment post-application? Were the windows open or closed? When did they shower? Were they also exposed elsewhere, for example at work?

The wide range of exposure estimates and the vast uncertainty associated with any estimate makes it impossible to identify an actual dose estimate that is linked to the rather small change in working memory observed in the CCCEH study. The fact that EPA's response to the SAP report – which highlighted in a negative way the "inability to either know, or confidently make assumptions about, aspects of exposure patterns, labor and delivery, and blood collection" and the "the lack of knowledge of the sensitive window(s) of exposure during pregnancy" – was to derive dose reconstruction estimates based on absolutely no data related to the cohort members' timing of exposure or sensitive windows, indicates a misunderstanding of the SAP's concerns. The SAP went on to criticize reliance on the CCCEH study, because the data showed "a lack of a clear dose-response relationship and evidence of temporality (i.e., two key concepts in pharmacology and toxicology)." Abandoning the CCCEH cord blood exposure data in favor of EPA's dose reconstruction estimates, which are completely devoid of actual connection to the CCCEH cohort, exacerbates this SAP concern instead of mitigating it.

In addition, EPA is using an inappropriately high level of conservatism in its dose-reconstruction effort given that its stated goal is to derive a lowest observed adverse effect level (LOAEL) dose. In the latest risk assessment, EPA references an earlier dose reconstruction that was part of the 2014 Revised Human

Health Risk Assessment (2014 HHRA). The goal of the 2014 HHRA exercise was to estimate an "upper limit, bounding level exposure" and as a result it contained very conservative assumptions with regards to exposure duration and bathing frequency. By contrast, EPA states that the purpose of the dose reconstruction in its latest risk assessment is to predict "typical" product usage and behaviors, and therefore the assumptions are essentially realistic or even tend to underestimate exposure (e.g., daily shower taking place immediately after application; exposure duration of only 2 hours/day). However, EPA should be estimating upper limit exposures if its goal is to derive a LOAEL dose. Assuming for a moment that the CCCEH study did observe an actual association between chlorpyrifos exposure and change in working memory, only the most highly exposed cohort members would have experienced this adverse effect. Most cohort members were exposed to comparatively lower levels of chlorpyrifos, which did not cause a change in working memory. Therefore, exposure resulting from "typical" product usage and behaviors should not be expected to cause a response, and if used at all should be considered a no observed adverse effect level (NOAEL) dose, not a LOAEL dose. Instead, upper limit exposures, representing the most highly exposed individuals within the CCCEH cohort, would have been the only doses to be potentially associated with an adverse effect.

Taking a step back, USDA wishes to highlight a logical flaw in EPA's reasoning. In its dose reconstruction, EPA considered the exposure from the monthly residential crack-and-crevice application to be the only contributor to the chlorpyrifos doses experienced by the CCCEH cohort. In other words, EPA is assuming that the crack-and-crevice application, and only the crack-and-crevice application, is causing any adverse effects potentially observed in the CCCEH study cohort, such as a change in working memory. By implication, this indicates that the Agency considers any dietary (food or drinking water) exposure to chlorpyrifos among the CCCEH cohort to be negligible. As EPA points out in its latest risk assessment, all residential uses of chlorpyrifos were cancelled in 2000, meaning that today the only relevant exposures for the general population are food and drinking water exposures. There is no reason to believe that the population today is exposed to significantly higher levels of chlorpyrifos in the diet than the CCCEH cohort was. How then is it possible that food and drinking water exposures were not even considered in the CCCEH cohort dose reconstruction, but EPA now claims that food exposure *alone* causes some individuals to exceed the acceptable level of chlorpyrifos exposure by as much as 140 times?

Conclusion for Substantive Concerns

EPA's latest risk assessment depends on three conclusions related to the existence of a health effect, causality, and the dose-reconstruction approach. For EPA's assessment to be meaningful, all three conclusions would have to be well-supported by the evidence and logically coherent. Instead, they range from questionable to unsupported by the evidence to incorrect. As a result, the latest risk assessment fails to show either a causal or a dose-response relationship between chlorpyrifos exposure and a change in working memory among the CCCEH cohort, even though causality and the existence of a dose-response relationship are two fundamental pillars of regulatory toxicology and risk assessment. USDA concludes by asking whether, before November 2016, EPA has ever derived a point of departure for pesticide risk assessment based on a single study which the Agency has concluded does not contain *any* usable dose data.

Procedural Concerns

USDA strongly urges EPA to abandon use of the CCCEH study to set a point of departure for chlorpyrifos and to return to using AChEI as the critical effect. If EPA chooses to continue to use the CCCEH study, EPA's latest risk assessment should be re-submitted to the SAP for review. USDA finds this to be absolutely crucial for maintaining public confidence in the pesticide regulatory process. Compared to the March 2016 risk assessment that the SAP reviewed, the latest risk assessment is even

further beyond the "mainstream" of pesticide risk assessment. Mostly, this is due to the dose reconstruction approach that, to USDA's knowledge, has never been externally reviewed. In addition, the fact that the latest risk assessment continues to be based on the CCCEH study clearly weighs in favor of allowing the SAP to review again, in order to determine whether its earlier criticisms of the CCCEH study have been addressed or mitigated.

USDA notes that according to EPA's Peer Review Policy, "external peer review is the approach of choice" for influential scientific information intended to support important decisions. Influential scientific information in turn is characterized, inter alia, by its establishment of a significant precedent, model, or methodology; its material adverse effect on the economy or a sector of the economy; its addressing of significant controversial issues; its significant interagency implications; and its consideration of an "innovative" approach for a previously defined problem (EPA Peer Review Handbook, 4th Ed.). In USDA's opinion, all of these factors are present in EPA's latest chlorpyrifos risk assessment, indicating that an external peer review of the document is warranted. USDA commends EPA for having consulted the SAP three times already on the subject of chlorpyrifos. However, this latest hybrid approach is more than just a refinement or an implementation of previous SAP recommendations. A completely new risk assessment approach is being considered which will have a wide impact on the evaluation chlorpyrifos, as well as other pesticides in the future. USDA strongly urges EPA to present this latest risk assessment to the SAP. Before doing so, EPA should thoughtfully consider and publicly respond to all public comments received on the subject of chlorpyrifos since the 2014 Revised Human Health Risk Assessment was published. This will allow the public to provide an informed opinion at the next SAP meeting, and it will help the SAP in fully understanding the breadth of risk assessment approaches considered by the Agency.

USDA is aware that EPA is under a court-ordered deadline to fully respond to the PANNA/NRDC petition (by issuing a final rule, if necessary) by March 31, 2017. However, USDA strongly feels that EPA should take the necessary time to fully address the SAP concerns and to develop a robust risk assessment. To that end, USDA requests that EPA issue an order denying the petition to revoke chlorpyrifos tolerances and cancel uses. This would allow the Agency to continue its evaluation of chlorpyrifos as part of the ongoing pesticide review process and free from undue litigation-induced pressure, and would not preclude the Agency from taking mitigation action in the future if neurodevelopmental effects related to chlorpyrifos are identified and confirmed.